1. TITLE PAGE

Protocol Title:
Idebenone in Patients with Primary Progressive Multiple Sclerosis Open-Label Extension (IPPoMS-E)
Protocol Number: **13-N-0088**
Date of This Submission/Version: June 1, 2018

Principal Investigator

Name, Degree	Branch/Institute	Bldg/Rm	Phone	E-mail
Bibiana Bielekova, MD	NIB/NINDS	10/5C103	301-402-4488	bielekovab@ninds.nih.gov

Lead Associate Investigator

Name, Degree	Branch/Institute	Bldg/Rm	Phone	E-mail
Alison Wichman, MD	NIB/NINDS	10/5C101	301-496-0064	wichmana@ninds.nih.gov

Associate Investigators

Name, Degree	Branch/ Institute	Bldg/Rm	Phone	E-mail
Mary Alice Sandford, RN, CRNP	NDU/NINDS	10/5C103	301-496-4747	maryalice.sandford@nih.gov
Jenifer Dwyer, RN	Clinical Center	10/5C101	301-496-0064	JDwyer@cc.nih.gov
Laura Kannaian, RN	NDU/NINDS	10/5C103	301-496-0586	kannaianl@cc.nih.gov
Tanya Lehky, MD	NINDS	10-CRC/7-5680	301-496-7428	lehkyt@mail.nih.gov
Govind Bhagavatheeshwaran, PhD	NIB/NINDS	10/5C103	301-402-6391	bhagavatheeshg@ninds.nih.gov
Rosalind Hayden, RN	OCD/NINDS	10/5C101	301-827-9002	haydenre@ninds.nih.gov
Elena Romm, MS	NIB/NINDS	10/5C103	301-594-2697	RommE@ninds.nih.gov

Research Contact

Name, Degree	Branch/Institute	Bldg/Rm	Phone	E-mail
Laura Kannaian, RN	NDU/NINDS	10/5C103	301-496-0586	kannaianl@cc.nih.gov

Medical Advisory Investigator

Name, Degree	Branch/Institute	Bldg/Rm	Phone	E-mail
Bibiana Bielekova, MD	NIB/NINDS	10/5C103	301-402-4488	bielekovab@ninds.nih.gov

Total requested accrual
85 Patients
0 Volunteers

Project Uses Ionizing Radiation: ☐ No ☒ Yes
☐ Medically-indicated only
☒ Research-related only
☐ Both

IND/IDE ☐ No ☒Yes *(attach FDA documentation)*
Drug/Device/# 104,895
Sponsor: National Institute of Neurological Disorders and Stroke (NINDS), Dr. Bielekova

Durable Power of Attorney ☒ No ☐ Yes
Multi-institutional Project ☒ No ☐ Yes
Institution_____ FWA #_____
Date of IRB approval: n/a

Data and Safety Monitoring Board ☐No ☒ Yes

Technology Transfer Agreement ☐ No ☒ Yes
Agreement type and number: MCRADA #2012-0244
Expiration Date: *12/5/2020*

Confidential Disclosure Agreement ☐ No ☒ Yes

Samples are being stored ☐ No ☒ Yes

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3. PRECIS

3.1 Objective:

A Phase I/II clinical trial is being conducted to investigate the safety, therapeutic efficacy and mechanism of action of idebenone in primary-progressive multiple sclerosis (PP-MS) patients (IPPoMS (Protocol Number 09-N-0197)). Patients who have completed the 2-year treatment period of IPPoMS, may enter into this open-label extension study (IPPoMS-E) if they are found to be eligible by the Investigator and desire treatment with idebenone despite remaining blinded as to their allocation to active treatment versus placebo during the IPPoMS trial. The aim of this open-label extension study is gather additional data on safety, efficacy and effects of idebenone on CSF biomarkers in these patients over a period of 1 year. This study will provide open-label idebenone for patients with PP-MS, previously randomized to idebenone or to placebo in the blinded phase of IPPoMS.

3.2 Study Population:

Patients who were previously enrolled in the IPPoMS (Protocol Number 09-N-0197) will be invited to participate in the trial. The same idebenone dose used in the randomized clinical trial (2250 mg/day) will be used in this study.

3.3 Design:

This is a single group, open-label safety and efficacy extension trial with a one year treatment period. Patient-specific biomarkers of disease progression, CSF biomarkers of oxidative stress, longitudinal neuroimaging including quantitative measures of CNS tissue destruction and clinical data will be collected as in the randomized study.

3.4 Outcome Measures:

The measurement and collection of data will be performed as in the randomized trial. Quantitative neuroimaging measures of central nervous system (CNS: i.e. brain and spinal cord) tissue destruction and clinical and functional measures of neurological disability will be collected every 6-12 months. Additionally, biomarkers focusing on analysis of reactive oxygen species (ROS) and oxidative stress will be collected every 12 months. The primary outcome measure defined in the IPPoMS trial will be also utilized in IPPoMS-E. For patients originally randomized to placebo, patient-specific slopes of disease progression during 2 years of placebo therapy (as measured by primary and secondary outcomes) will be compared to patient-specific slopes of disease progression during 1 year of open label idebenone therapy. Combination of IPPoMS and IPPoMS-E trials will significantly expand paired “no therapy” vs. “idebenone therapy” CSF samples for biomarker studies. It will also provide (for the subgroup of subjects who were originally randomized to idebenone) longitudinal CSF samples on idebenone therapy (collected 2 years apart). This will allow calculations of intra-individual changes in CSF biomarkers on and off idebenone therapy, which may provide important insight into the mechanism of action of idebenone in PP-MS.

4. INTRODUCTION/SCIENTIFIC RATIONALE

4.1 Multiple Sclerosis (MS)

Multiple sclerosis (MS) is an inflammatory and demyelinating disorder of the central nervous system (CNS) that destroys myelin, oligodendrocytes, axons and neurons *(Noseworthy, Lucchinetti et al. 2000)*. The vast majority of newly diagnosed MS patients develop the relapsing-remitting form of the disease (RR-MS), in which periods of neurological worsening are followed by periods of spontaneous remission, at least at the beginning of the disease process. About 10-15% of patients develop primary-progressive MS (PP-MS), characterized by progressive accumulation of neurological disability from the disease onset, without any superimposed worsening (i.e. relapses) or improvements (remissions) *(Miller and Leary 2007)*.

The etiology of MS remains unclear, but disease develops in genetically susceptible individuals exposed to environmental triggers. The long favored hypothesis in MS has been formulated based on data obtained in the animal model Experimental Autoimmune Encephalomyelitis (EAE). This hypothesis implicates autoreactive, myelin-targeting CD4+ T cells generated in the periphery that access the CNS, where they induce an inflammatory cascade that results in the injury of previously normal neural tissues *(Sospedra and Martin 2005)*. However, in contrast to EAE, neither the target(s) of the immune response nor the cells of the immune system responsible for CNS damage have been identified in MS.

4.2 Primary progressive MS (PP-MS)

PP-MS patients differ from RR-MS patients in several important characteristics: 1. They tend to be older at the time of disease onset (mean 40 vs. 30 years); 2. Males and females tend to be affected equally; 3. Clinically there is a high prevalence of cortico-spinal dysfunction characterized by progressive weakness and spasticity *(Laule, Vavasour et al. 2010)*; 4: Patients have more prominent involvement of the spinal cord *(Bieniek, Altmann et al. 2006)* and generally lower amount of distinct white matter lesions (i.e. plaques) in the brain and less evidence for brain inflammatory activity *(Lucchinetti and Bruck 2004)* and, most importantly: 5: PP-MS patients do not respond to immunomodulatory therapies with proven efficacy in RR-MS *(Leary and Thompson 2005)*.

However, there are also some key similarities between PP-MS, RR-MS and secondary-progressive MS (SP-MS; the disease subtype that usually evolves after several years of untreated RR-MS): 1. Age of onset of the progressive phase is virtually identical between PP-MS and SP-MS (~40 years) (Ebers 2004); 2. Genetic background (e.g. HLA and IL-7Rα association *(Booth, Arthur et al. 2005)*) seems to be common to all 3 subtypes; an observation that is further supported by the fact that different disease types can occur within a single family; 3. Patients with all MS subtypes (~90% of RR-MS and 70-80% of PP-MS patients) have evidence for humoral immune responses in the CNS that are increased compared to the serum, or are entirely specific for the intrathecal environment (i.e. increased CSF IgG index and oligoclonal bands (OCB)) *(Miller and Leary 2007)*.

These differences and similarities underlie two major hypotheses about the relationship between PP-MS and RR/SP-MS: while some authors propose these diseases are simply phenotypical variants of

the identical disease process, others believe that PP-MS represents a distinct degenerative form of the disease, in which the immune response may not be primarily driving the disease pathogenesis. The latter hypothesis is indirectly supported by the "MS disease heterogeneity concept", in turn backed by pathological data indicating the mechanism of active demyelination seems different between different patients, but identical for all MS lesions within single subjects. Four pathological subtypes have been identified *(Lucchinetti, Bruck et al. 2000)*, two of which probably represent immune-mediated pathology, whereas in the other two pathological patterns immune cells are much less conspicuous and degenerative pathophysiology may predominate *(Lucchinetti, Bruck et al. 2000)*. Specifically, pattern IV demyelination, called "oligodendrocyte degeneration in periplaque white matter", with evidence of apoptosis of oligodendrocytes and paucity of T/B lymphocytes, is almost exclusively observed in PP-MS patients. Nevertheless, PP-MS patients were also observed to have pathological patterns I and II, i.e. those where presumed mechanisms of acute demyelination are T cell/macrophage-mediated and Ab/complement-mediated, respectively.

Part of the pathophysiological controversy may reside in our inability to correctly classify patients. Complete reliance on clinical characteristics makes the classification highly dependent on the patient's ability to recollect transient neurological deficits that may have occurred years before the onset of progressive disease. Additionally, if MS lesions developed in clinically silent areas, even if associated with inflammation, they would not cause clinical deficit and therefore would not alert the patient or clinician of the occurrence of a relapse. As a result, reliance on purely clinical criteria will inevitably lead to inclusion of a more heterogeneous patient population in the PP-MS category. One of the hallmarks of inflammatory lesions in RR-MS is their association with the breakdown of the blood-brain barrier (BBB), which can be visualized as contrast-enhancing lesions (CELs) on MRI. Although PP-MS patients generally have a significantly lower number of CELs *(Ingle, Stevenson et al. 2003)*, patients with CELs have been classified as PP-MS based on clinical criteria *(Filippi, Campi et al. 1995)* and have been included in clinical trials of immunomodulatory therapies *(Wolinsky, Narayana et al. 2007)*. Not unexpectedly, it is precisely these PP-MS patients that were shown to benefit from applied immunomodulatory therapy in subgroup analysis *(Wolinsky, Narayana et al. 2007)*. This is very reminiscent of our experience with effectiveness of immunomodulatory therapies for SP-MS *(Kappos, Weinshenker et al. 2004)*. The results of these trials suggest that while currently available immunomodulatory therapies effectively target that part of the MS disease process characterized by formation of focal CELs, they are much less effective in slowing down a more diffuse, degenerative process, which underlies the development of disability in non-inflammatory PP- and SP-MS.

4.3 Mechanisms of tissue injury in PP-MS

Both new imaging modalities *(Filippi, Rocca et al. 2002; Dehmeshki, Chard et al. 2003; Filippi 2003; Narayana, Wolinsky et al. 2004; Sastre-Garriga, Ingle et al. 2004; Rovaris, Gallo et al. 2005; Sastre-Garriga, Ingle et al. 2005; Ramio-Torrenta, Sastre-Garriga et al. 2006; Khaleeli, Sastre-Garriga et al. 2007; Manfredonia, Ciccarelli et al. 2007; Rovaris, Judica et al. 2008)* and pathological data *(Lucchinetti and Bruck 2004; Kutzelnigg, Lucchinetti et al. 2005)* suggest that in PP-MS, CNS pathology is more diffuse *(Filippi, Rocca et al. 2002; Dehmeshki, Chard et al. 2003; Filippi 2003; Narayana, Wolinsky et al. 2004; Ramio-Torrenta, Sastre-Garriga et al. 2006; Khaleeli, Sastre-Garriga et al. 2007; Manfredonia, Ciccarelli et al. 2007; Rovaris, Judica et al.*

2008) and occurs to some extent independently of focal lesions *(Sastre-Garriga, Ingle et al. 2004; Kutzelnigg, Lucchinetti et al. 2005; Rovaris, Gallo et al. 2005)*. The cervical spinal cord is the major target of the disease process in PP-MS, underlying most of the clinical disability *(Ingle, Stevenson et al. 2003)*. The diffuse CNS process in PP-MS is characterized by microglial activation and diffuse axonal injury in the white matter *(Kutzelnigg, Lucchinetti et al. 2005)* and by cortical demyelination and neuronal loss in the gray matter *(Kutzelnigg, Lucchinetti et al. 2005)*. This is consistent with new observations from optical coherence tomography (OCT), which demonstrated significant reduction in the inner nuclear layer, consistent with the presence of primary retinal pathology only in PP-MS, but not RR-MS or SP-MS subtypes *(Albrecht, Ringelstein et al. 2012)*. Additionally, low level but persistent endothelial abnormalities and BBB leak, both in normal appearing white and gray matter have been observed *(Leech, Kirk et al. 2007)*.

Accumulating data indicate that oxidative stress and mitochondrial dysfunction may play a major role in the pathogenesis of MS, especially in the progressive stages *(Gionchetti, Campieri et al. 1994; Greco, Minghetti et al. 1999; Bizzozero, DeJesus et al. 2005; Dhib-Jalbut, Arnold et al. 2006; Koch, Ramsaransing et al. 2006; Koch, Mostert et al. 2007)*. MS patients have increased lipid peroxidation products in the CSF *(Hunter, Nlemadim et al. 1985; Naidoo and Knapp 1992; Keles, Taysi et al. 2001)*; presence of 3-nitrotyrosine in demyelinated lesions *(Liu, Zhao et al. 2001)*; evidence of nitrosative damage in the normal-appearing white matter *(Bizzozero, DeJesus et al. 2005)* and increased levels of carbonyl in both white and gray matter *(Bizzozero, DeJesus et al. 2005)*. These findings were confirmed on brain tissue derived from 18 MS patients with progressive disease (SP-MS and PP-MS), where the authors demonstrated severe oxidative damage to proteins, nucleic acids and lipids, predominantly in the MS lesions and to a milder degree also in normal appearing WM *(van Horssen, Schreibelt et al. 2008)*. In terms of cellular localization, most of the oxidized lipids, proteins and nucleic acids were detected in reactive astrocytes and in myelin-laden macrophages. Detected oxidative stress/damage was associated with strong upregulation of Nrf2/ARE-regulated antioxidant enzymes, such as superoxide dismutase-1 and -2, catalase and heme oxygenase-1. Again, these enzymes were upregulated predominantly in reactive astrocytes and foamy macrophages. These data indirectly suggest that reactive astrocytes and macrophages that phagocytosed myelin debris are the main cell types involved in detoxification of ROS and that astrocytes, through expression of Nrf2-ARE enzymes play a pivotal role in the maintenance of redox homeostasis under inflammatory CNS conditions *(van Horssen, Schreibelt et al. 2008)*. Oligodendrocytes and brain endothelial cells had remarkably low expression of antioxidant enzymes *(van Horssen, Schreibelt et al. 2008)*; a finding that supports previous studies indicating that oligodendrocytes are extremely sensitive to oxidative stress due to their impaired antioxidant defense mechanism *(Juurlink, Thorburne et al. 1998)*. Other studies suggested that MS patients may have diminished resistance to oxidative stress, as the levels of antioxidants were found to be diminished in the brain *(Langemann, Kabiersch et al. 1992; Bizzozero, DeJesus et al. 2005)* and blood *(Zagorski, Dudek et al. 1991; Syburra and Passi 1999)* of MS patients.

There are two major sources of reactive oxygen species (ROS) in the brain: 1. the respiratory burst of immune cells mediated by NADPH oxidases and 2. the electron-transport chain of mitochondria. In the intrathecal compartment of MS patients, only cells of myeloid lineage (i.e. microglia, monocytes/macrophages and myeloid dendritic cells) can mediate oxidative burst, because granulocytes are not present in MS lesions and oxidative burst of lymphocytes is 1000 fold lower than oxidative burst of myeloid cells. When cells of myeloid lineage become activated, they not only

produce ROS, but also secrete soluble factors, such as IL-12p40 and CXCL13. These soluble factors can be detected in the CSF as a biomarker of activated immune cells of myeloid lineage. In order to assess contribution of oxidative burst versus failing mitochondria to ROS generated in the intrathecal compartment of subjects with different MS subtypes, we measured CSF levels of lipid peroxidation product, 4-hydroxy-nonenal (4-HNE), IL-12p40 and CXCL13 in a large group of untreated subjects who presented for the diagnostic work-up of neuroimmunological diseases (Figure 1). We observed elevated levels of 4-HNE in all subjects with MS, but reaching statistical significance only in the PP-MS cohort. On the other hand, biomarkers of activation of myeloid lineage, i.e. IL-12p40 and CXCL13, were elevated only in RR-MS patients, and subjects with other inflammatory neurological diseases (OIND), but not in PP-MS patients. Therefore, we conclude that while oxidative burst contributes to the intrathecal oxidative stress in RR-MS patients, mitochondrial dysfunction is the main source of CSF ROS in PP-MS patients.

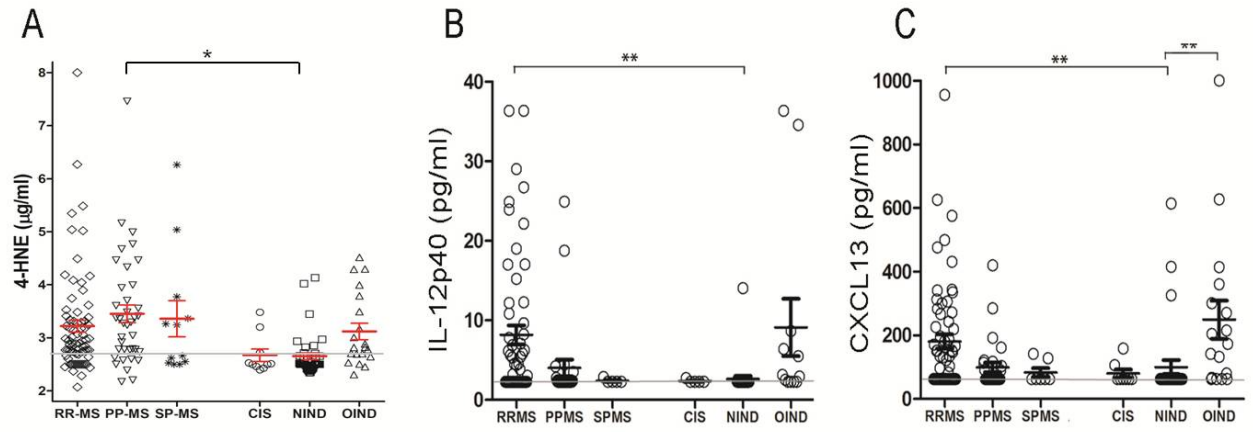

Figure 1:
CSF levels of lipid peroxidation product 4-hydroxy-nonenal (4-HNE) and IL-12p40 and CXCL13 measured in the blinded fashion in a large cohort of MS patients and controls (N=167).
CIS = clinically isolated syndrome patients who did not progress to definite MS within 1 year of follow-up, NIND = non-inflammatory neurological disorders, OIND = other inflammatory neurological disorders. * $p<0.05$, ** $p<0.001$

Mitochondria themselves may be the target of the oxidative damage in MS lesions *(Lu, Selak et al. 2000)* and profound mitochondrial dysfunction was found in the gray matter of MS patients *(Dutta, McDonough et al. 2006)*. Specifically, functional activities of mitochondrial electron transport chain (ETC) complexes I and III were decreased in MS motor cortex and this reduced mitochondrial gene expression was specific for neurons *(Dutta, McDonough et al. 2006)*. Furthermore, multiple investigators documented accumulating presence of mitochondrial DNA mutations and existence of respiratory-deficient mitochondria in neurons *(Kiryu-Seo, Ohno et al. ; Lu, Selak et al. 2000; Andrews, Nichols et al. 2005; Kidd 2005; Dutta, McDonough et al. 2006; Campbell, Ziabreva et al. 2011; Campbell and Mahad 2012; Campbell, Ohno et al. 2012).*
On the other hand, specifically in the acute MS lesions with characteristics of pathological subtype III, severe mitochondrial deficiencies have been observed both in oligodendrocytes and astrocytes (Mahad, Ziabreva et al. 2008; Mahad, Ziabreva et al. 2009).
It is hypothesized that mitochondrial dysfunction, which generally increases with age, may contribute, if not underlie the development of progressive stage of MS *(Andrews, Nichols et al. 2005)*. This hypothesis is based on several published observations:

1) Acute demyelination leads to conduction block and resultant compensatory distribution of Na channels from the node of Ranvier along the entire demyelinated segment. In addition to this topographic redistribution of Na channels, demyelinated axons revert to a stage seen in immature axons, with preferential use of $Na_v1.2$ instead of $Na_v1.6$ channels *(Black, Kocsis et al. 1990)*.
2) This switch in Na channel usage and their redistribution, while allowing conduction along the demyelinated axon, is energetically extremely demanding, requiring a large number of ATP molecules to sustain the Na^+/K^+-ATPase pump, which is necessary to maintain the resting membrane potential *(Black, Kocsis et al. 1990; Black, Newcombe et al. 2007)*. This high energy demand is indirectly reflected by the observed redistribution of mitochondria along demyelinated axons *(Mutsaers and Carroll 1998)* and associated axonal swelling.
3) Presence of inflammation further exaggerates this energy deficiency of demyelinated axons, because some of the inflammatory mediators (e.g. NO) are known to inhibit the mitochondrial respiratory chain *(Bolanos, Almeida et al. 1997)*.
4) However, even in the absence of inflammation, it would be predicted that mitochondria would not be able to sustain the non-physiologically high energy demand of chronically demyelinated axons long-term. It is known that even during the natural aging process, mitochondrial DNA accumulates mutations and energy production of aging mitochondria diminishes in time. When demyelination becomes widespread and sustained, as in progressive MS, then resultant increased energy requirement cannot be sustained by actual ATP production. This leads to "virtual hypoxia*" (Lassmann 2003)*, which initiates vicious circle of enhanced generation of ROS by failing mitochondria, resulting in progressive oxidative damage of mitochondrial DNA, proteins and lipids. Damaged mitochondria show impairment of oxidative phosphorylation, decreased rate of electron transfer, decreased enzymatic activities and are also thought to produce higher levels of ROS. This, in the absence or deficiency of an effective endogenous detoxification system, would lead to further oxidative damage of mitochondrial DNA and associated lipids and proteins. Mitochondrial DNA is especially susceptible to oxidative damage due to lack of protective histones and less efficient repair mechanisms *(Mecocci, MacGarvey et al. 1993)*.
5) Decline in ATP production leads to accumulation of unfolded proteins in the endoplasmic reticulum (ER), because proper oxidative folding of proteins requires overcoming thermodynamically unfavorable intermediates though ATPase activities of ER chaperones. Resulting ER stress activates unfolded protein response (UPR), which is part of cellular integrated stress response (ISR). UPR/ISR leads to cellular adaptations that may lead to restoration of homeostasis, but only if ATP production can be restored, at least to the levels that support ATPase activities of ER chaperones. Only then can misfolded proteins be degraded, both from ER and mitochondria *(Hu and Liu 2011)*. While respiratory-deficient mitochondria are degraded by combination of mitochondrial fission/fusion and mitophagy *(Twig and Shirihai 2011),* restored production of proteins and lipids by ER can then lead to assembly of fully functional mitochondria.
6) The resultant lack of ATP would lead to increased intra-axonal Na^+ and subsequent increase in intra-axonal Ca^{2+} via reversal of the Na^+/Ca^{2+} exchanger and enhanced Ca^{2+} release from ER. Additionally, Ca^{2+} is also selectively transferred from the ER to mitochondria, in order to stimulate ATP production, as early adaptation mechanism of ER stress. However, with underlying mitochondrial dysfunction, this adaptation may not lead to enhanced ATP production, but rather to mitochondrial-induced apoptosis. Thus, resultant damage to the

demyelinated axon would be a combination of oxidative damage with Ca^{2+}-mediated excitotoxicity, leading to programmed cell death.

There is additional evidence that supports the hypothesis of mitochondrial dysfunction underlying axonal degeneration in MS: CSF concentrations of sorbitol, fructose and lactate (all metabolites of extramitochondrial glucose metabolism) were found to be elevated in MS, especially in progressive stages and to correlate with clinical measures of disability *(Regenold, Phatak et al. 2008)*. Because extra-mitochondrial glucose metabolism increases with impaired mitochondrial metabolism of glucose, these findings strongly implicate mitochondrial dysfunction in the pathogenesis of progressive stages of MS. Of interest to this study, the intraventricular lactate can be measured serially in-vivo by MRS *(Kaufmann, Shungu et al. 2004)*, although this methodology has not been applied to MS to our knowledge.

4.4 Therapeutic options for PP-MS patients

There are currently no treatments with proven therapeutic efficacy for PP-MS *(Leary and Thompson 2005)*. Neither interferon-beta preparations *(Leary, Miller et al. 2003; Montalban 2004)* nor glatiramer acetate *(Wolinsky, Narayana et al. 2007)* has been able to slow down the accumulation of disability in PP-MS. Several Phase II trials of Mitoxantrone in PP-MS were initiated, but none reported positive effects *(Leary and Thompson 2005)*. A recently reported large multi-center, placebo-controlled Phase II trial of Rituximab in PP-MS also failed to demonstrate any effect on the accumulation of disability in this patient population *(Hawker, O'Connor et al. 2009)*.

These data collectively indicate that therapies targeting the immune system and specifically the formation of Gd-enhancing MS lesions do not demonstrate beneficial effect in PP-MS. In agreement with the reviewed hypothesis that the pathophysiology of PP-MS may rely more on neurodegenerative, rather than immune-mediated mechanisms of CNS tissue destruction, a pilot trial of the neuroprotective agent riluzole showed a mild effect on inhibiting the development of cervical cord atrophy in the PP-MS cohort *(Kalkers, Barkhof et al. 2002)*, however, it did not reach statistical significance.

4.5 Idebenone pharmacokinetic, pharmacodynamic and toxicity data

Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone) is a synthetic analogue of coenzyme Q10, which is an indispensable constituent of the mitochondrial electron-transport chain (ETC) and also cell membrane antioxidant.

After oral administration, idebenone undergoes rapid and extensive metabolism, whereby >99% of idebenone is converted to metabolites by first pass metabolism. In the initial steps of metabolism, the side chain of idebenone undergoes a process of oxidative shortening leading to the metabolites QS10, QS8, QS6 and QS4 (the number refers to the number of carbon atoms in the side-chain). Idebenone and all of the short-chain metabolites are modified further by conjugation (glucuronidation or sulfatation) resulting in conjugated forms of idebenone (Idebenone-C (IDE-C)) as well as QS10-C, QS8-C, QS6-C and QS4-C.

Bioanalytical methods allow measurement of either

- idebenone and unconjugated metabolites (idebenone, QS10, QS6, QS4)
- or the combined measurement of conjugated molecules plus unconjugated forms of the same molecules, referred to as 'IDE+IDE-C', 'QS10+QS10-C', ' QS6+QS6-C ' and ' QS4+QS4-C ', respectively.

4.5.1. Preclinical studies:

The pharmacology and toxicology of idebenone have been studied extensively in animals and humans *(Gillis, Benefield et al. 1994)*. These studies are described fully in the Investigator's Brochure (Appendix G) and are summarized below:

In rats and dogs oral idebenone is rapidly absorbed and extensively metabolized in the intestinal mucosa and liver. The primary route of metabolism is β-oxidative shortening of the side chain. The major metabolites are QS10, QS8, QS6, and QS4 (where 10, 8, 6 and 4 denote the number of carbon atoms in the side chain). Glucuronide and sulfate conjugates of these metabolites are also formed. In rats, idebenone is 91% absorbed and 90-94% protein bound. The T_{max} of idebenone is 0.25 hours and the half-life is 4.5 hours. In dogs, idebenone is 62% absorbed and 99% protein bound. The Tmax is one hour and levels show a biphasic decline with half-lives of 2.2 and 15.4 hours, respectively. In dogs, plasma levels were broadly dose-dependent and variable but were consistently increased in fed animals. There was no evidence of accumulation of idebenone or metabolites. In both rats and dogs, oral idebenone was completely excreted within 48 hours, distributed evenly between urine and feces.

The acute oral toxicity of idebenone was low (> 10,000mg/kg in mice and male rats; ~10,000 mg/kg in female rats). Chronic oral toxicity studies in rats and dogs have been published (*Spicer and Wazeter 1985; Suhara, Chiba et al. 1985)*. Treatment related adverse effects were limited to local irritant effects mainly in the forestomach (a rodent-specific organ) in the rat and to clinical gastrointestinal effects (loose feces/diarrhea and emesis), without any pathological changes, in the dog. It can therefore be considered that no adverse effects of clinical relevance were observed at the highest dose used in these studies (500mg/kg/day) *(Spicer and Wazeter 1985; Suhara, Chiba et al. 1985).* Results from toxicity studies conducted by Santhera, including a 39-week toxicity study in fed dogs, are consistent with the findings of published Takeda studies, indicating that the drug substance used by Santhera has a similar safety profile as the Takeda material. In a 4 week study in rats and a 39-week study in fed dogs, at Cmax, concentrations of idebenone in plasma were 21 – 22 times higher in the rat, and 25 – 28 times higher in the dog, when compared with the maximum mean concentration observed in humans receiving idebenone 2250 mg. For AUC_{0-t} safety margin ranges of 16 – 22 in the rat and 20 - 22 in dogs were calculated, when steady state exposure at the no adverse effect levels is considered for each species. Taken together, the toxicokinetic data reported here indicate that a sufficient safety margin exists between exposure in humans at a daily dose of 2250 mg/day of idebenone and exposure in rats and dogs, at doses which had no toxic effects relevant to safe use in humans.

Idebenone was not genotoxic in *in-vitro* bacterial reverse mutation assays and *in-vivo* mouse micronucleus studies. A positive clastogenic effect was observed in an in vitro chromosome aberration test at very high concentrations (7500ng/ml and above) (RCC-CCR 871902). This effect

is not considered to pose a risk for clinical trial subjects in view of the high concentrations at which effects were observed and in view of the negative in vivo response on the mouse micronucleus test.

Idebenone at doses up to 500mg/kg/day had no adverse effects on fertility and reproductive performance in rats. Idebenone administered at doses up to 500mg/kg/day in the rat and up to 150mg/kg/day in the rabbit during the period of organogenesis had no teratogenic or embryo-fetal toxic effects. Doses up to 500mg/kg/day administered during late pregnancy and lactation had no adverse effects on the dams or on the post partum development of the pups.

4.5.2 Clinical studies

In healthy volunteers, idebenone is well tolerated when given as single oral doses up to 1050mg (SNT-I-004) or as multiple oral doses of 2250mg/day (750mg TID) for 14 days (SNT-I-003).

Idebenone has been extensively studied as a potential therapeutic agent for neurological diseases, including Alzheimer's disease *(Gutzmann and Hadler 1998; Gutzmann, Kuhl et al. 2002)*, Huntington's disease *(Ranen, Peyser et al. 1996)*, Friedrich's ataxia (FRDA) *(Schols, Vorgerd et al. 2001; Artuch, Aracil et al. 2002; Rustin, Rotig et al. 2002; Buyse, Mertens et al. 2003; Mariotti, Solari et al. 2003; Artuch, Aracil et al. 2004; Rustin, Bonnet et al. 2004; Di Prospero, Baker et al. 2007; Pineda, Arpa et al. 2008)* and multi-infarct dementia. In these clinical trials, in which a variety of doses and dosing regimens were employed, idebenone was found to be safe and well tolerated. In phase I trials, idebenone was shown to be well tolerated at doses of 360 mg/day for 12 months, and at doses of 900 mg/day for four weeks. In a double-blind, placebo controlled trial of idebenone for the treatment of Huntington's disease, 100 patients were randomized to receive idebenone 90 mg three times per day or placebo for a period of 12 months. Ninety-one patients completed the study, and no patients left the trial for adverse events attributed to idebenone. Idebenone was found to be safe and well tolerated in this study, but no benefit was found *(Ranen, Peyser et al. 1996)*. Experience from the phase II and III clinical trials for Alzheimer's disease, in which patients received a 120 mg, 240 mg, or 360 mg three times per day for periods of up to 2 years, suggests a relatively benign toxicity profile for this drug. No therapeutic benefit was found. The most frequently cited adverse effects that occurred more often in the idebenone group were gastrointestinal symptoms such as anorexia, nausea, and diarrhea. Idebenone was marketed in Japan from 1986 to 1998 for the treatment of cognitive difficulties following stroke. During this period, idebenone was one of the most frequently prescribed drugs following stroke, with an estimated eight million patients treated. Idebenone was removed from the market in Japan after a post-marketing study failed to demonstrate efficacy, but remains registered for cognitive disorders in Italy, Portugal, Argentina and Ecuador.

No new issues of safety or tolerability have emerged in the course of the current Phase II and III clinical studies with idebenone in Friedreich's Ataxia (FRDA), Duchenne Muscular Dystrophy, and Leber's Hereditary Optic Neuropathy. Patients (8 years or older) received doses of idebenone ranging from 180 or 360 mg/day to 1350 or 2250 mg/day, depending on body weight, or placebo. Blood and urine laboratory analyses, vital signs and ECGs have not highlighted any safety concerns to date. Idebenone has been approved for the treatment of FA in Canada, is available under provisional approval for cardiomyopathy in FA in Switzerland, and can be obtained on a "named patient" basis in a number of other European countries, such as France, Italy, Belgium and Spain. Approximately 111.4 million tablets of idebenone were sold during the period 01 April 2004 – 31

March 2011. Assuming that three tablets irrespective of strength were taken daily for the whole period, the patient exposure to idebenone in these seven years was estimated to be 102,300 patient-years.

4.5.3 Pharmacokinetics and product metabolism in humans

Four Phase I studies were performed by Santhera, two single-dose studies, giving 150 mg idebenone or 7x150 mg idebenone to healthy male subjects after a standardized continental breakfast (Study SNT-I-002 and Study SNT-I-004), one two-way single dose study in two groups of healthy subjects to assess the effect of a fat-rich meal on the pharmacokinetics of idebenone 150 mg or 5x150 mg (Study SNT-I-001), and a two-week repeated dose study in two groups of healthy subjects to assess the effect of repeated dosing with either 150 mg t.i.d. or 5x150 mg t.i.d. (with the morning dose being given after a standardized continental breakfast) on the pharmacokinetics of idebenone (Study SNT-I-003). Furthermore two Phase I studies were performed at the NIH in FRDA patients *(Di Prospero, Baker et al. 2007; Di Prospero, Sumner et al. 2007)*. These studies are summarized below:

Overall conclusion of the Santhera Phase I program

Idebenone up to 1050 mg given as a single dose and up to 750 mg t.i.d (2250 mg) given as repeated doses for 14.3 days was well tolerated *(Bodmer, Vankan et al. 2009)*. The reported AEs are mainly gastrointestinal system disorders. There were no clinically relevant effects seen on hematological parameters or on biochemical parameters, in particular no effects were observed on renal or liver function or on lipid metabolism, including HDL and LDL cholesterol.

Frequent monitoring of ECG morphology and QTc duration in studies SNT-I-001 and SNT-I-003 covering the whole time interval in which idebenone was above the limit of quantification gave no clinically relevant abnormal findings, and in particular no prolongation of the QTc interval.

After administration, idebenone is immediately metabolized by side chain reduction to QS10, QS8, QS6, and QS4. Both idebenone and its metabolites are conjugated and then rapidly excreted, predominantly by the kidney. Parent compound (non-metabolized and non-conjugated) idebenone in plasma amounts to between 0.1% and 1% of total (conjugated plus unconjugated – IDE+IDE-C) idebenone, indicating a very high first-pass effect. Therefore the plasma concentrations of idebenone are very low even after relatively high doses, e.g. Cmax and AUC of idebenone after dosing of 2250 mg/day for two weeks are 19.2 ng/ml and 106.2 mg/L x hr respectively. The metabolites QS10+QS10-C, QS6+QS6-C and QS4+QS4-C were in the same order of magnitude as that of IDE+IDE-C. The pharmacokinetics of idebenone are linear as assessed indirectly by the amounts of IDE+IDE-C. Increasing the oral dose of idebenone five or seven fold results in corresponding increases in the AUC of IDE+IDE-C.

There is a food effect (3-7-fold increase), as assessed in study SNT-I-001, which is more pronounced at higher doses. Repeated daily dosing does not lead to relevant accumulation of the metabolites indicating no enzyme auto-inhibition. In addition, there is no indication that

idebenone metabolizing enzymes are induced. Because of the high first pass effect, the increase of bioavailability with food is considered to be beneficial. Therefore the dosing recommendation for idebenone in all studies is for the daily dose to be given in three administrations (t.i.d.) with a meal.

Overall conclusion on the NIH Phase I program in FRDA patients

Two studies have been performed by the NIH to establish the maximum tolerated dose of idebenone in children, adolescents and adults with Friedreich's ataxia when idebenone was administered as a single oral dose (Phase I A study) or as repeated oral doses (Phase I B study).

In both Phase I studies, PK characteristics of idebenone were assessed in children, adolescents and adults. In the single dose study, doses up to 75 mg/kg were administered. In the repeated dose study a dose of 60 mg/kg was administered for 1 month. In the repeated dose study no relevant differences for Cmax and AUC for IDE+IDE-C between the age groups were detected *(Di Prospero, Baker et al. 2007; Di Prospero, Sumner et al. 2007)*.

Idebenone was well tolerated. AEs reported were consistent with the known safety profile, with GI disturbances being the most frequent reported AEs for idebenone.

Studies in patients with impaired organ function

Two studies were performed in patients with impaired organ function (Reports CV2619/EC071 for hepatic; CV2619/EC070 for renal). As expected, patients with impaired renal function not undergoing hemodialysis, have higher C_{max} and AUC values of IDE+IDE-C and QS10+QS10-C than subjects with normal renal function, but patients with impaired renal function and undergoing hemodialysis have similar exposure values of IDE+IDE-C and only slightly higher values of QS10+QS10-C than subjects with normal renal function. These data are in agreement with the finding that the metabolites of idebenone are almost 80% eliminated by the kidney. The study also shows that IDE+IDE-C, and most probably also the other even more hydrophilic metabolites, can be eliminated by hemodialysis.

Patients with impaired hepatic function have higher exposure and longer elimination half-lives of IDE+IDE-C and QS10+QS10-C than subjects with normal liver function, indicating that the shortening of the side chain of idebenone is impaired.

Based on the results of the two studies, it is recommended that caution be exercised in patients with impaired renal function not undergoing hemodialysis. Idebenone is contraindicated in patients with impaired liver function.

Absorption of idebenone from the Takeda formulation, used in the NIH Phase I studies, and absorption from the Santhera formulation are similar, indicating no important differences in pharmacokinetic behavior between the formulations of the trial populations. Safety and tolerability were good in the published NIH studies and in the Santhera studies. Thus clinical safety/efficacy data and post-marketing experience available for the Takeda formulation can be considered to be relevant also to the Santhera formulation.

4.5.4 Product information

The study medication is manufactured by Santhera Pharmaceuticals and will be provided as 150 mg tablets.

The active compound, idebenone, is a yellow-orange crystalline material that melts at 52 to 54ºC. Idebenone is readily soluble in organic solvents but is practically insoluble in water. It is highly stable at room temperature. The molecular weight is 338.46. The complete description of active formulation is below:

Idebenone 150 mg film-coated tablets SNT-MC17/F02

Ingredients: idebenone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium povidone, magnesium stearate, silicon dioxide, film-coat: Opadry II 85F23495 (consisting of: aluminum lake, FD&C yellow #6, macrogol/PEG 3550, polyvinylalcohol, titanium dioxide, talc).

4.5.5 Storage and handling

Idebenone tablets are supplied in high density polyethylene (HDPE) bottles, and should be stored at room temperature (15- 25ºC) and must be protected from direct sunlight. Temperature excursions are permitted as follows: up to 30ºC for 12 months, up to 40ºC for 6 months.

4.6 Rationale for the use of Idebenone in PP-MS

As described above (Section 4.3: Mechanism of tissue injury in PP-MS), mitochondrial dysfunction together with aberrant formation of ROS are believed to underlie at least partially the development of progressive CNS tissue destruction in PP-MS. Idebenone has two key modes of action that make it an attractive therapeutic candidate for PP-MS:

1) Idebenone enhances the electron flow in the mitochondrial ETC. Specifically, idebenone can substitute for Coenzyme Q_{10} (CoQ_{10}) as an electron carrier and distribute the electrons between the various dehydrogenases and the cytochrome segments of the respiratory chain *(Sugiyama and Fujita 1985; Sugiyama, Fujita et al. 1985; Imada, Fujita et al. 1989; Geromel, Darin et al. 2002).* Perhaps more importantly, due to lower lipophylicity of idebenone in comparison to CoQ_{10}, idebenone (but not CoQ_{10}) can be reduced by cytosolic enzymes NAD(P)H:quinone oxidoreductases (NQO), which are significantly upregulated during oxidative stress, including in MS tissue *(van Horssen, Schreibelt et al. 2006).* Because NQO enzymes reduce idebenone in 2 electron step reaction, no semiquinone radical is generated. It is generation of the semiquinone intermediate that leads to production of ROS during mitochondrial electron transfer. Resultant cytosolic-mitochondrial shuttling of idebenone partially restores ATP production under conditions with impaired function of the ETC complex I *(Haefeli, Erb et al. 2011).* This mechanism is likely the explanation for the observed efficacy of idebenone in partially restoring visual function in patients with Leber's hereditary optic neuropathy (LHON; MIM 535000), a genetic condition with dysfunctional ETC complex I *(Klopstock, Yu-Wai-Man et al. 2011)*. Because mutations in mtDNA affecting ETC complex I *(Kalman, Lublin et al. 1995; Kalman, Laitinen et al. 2007; Campbell,*

Ziabreva et al. 2011), and resultant dysfunction of ETC complex I has been detected in MS brain tissue *(Andrews, Nichols et al. 2005; Dutta, McDonough et al. 2006; Campbell and Mahad 2012)* and in aging *(Stefanatos and Sanz 2011),* it is expected that idebenone may similarly potentiate ATP production in PP-MS subjects.

2) Idebenone functions as an anti-oxidant against membrane damage caused by lipid peroxidation, including lipid peroxidation that occurs in brain mitochondria *(Suno and Nagaoka 1984; Sugiyama, Fujita et al. 1985; Suno and Nagaoka 1989; McDaniel, Neudecker et al. 2005)*. However, it is unclear if the *in-vivo* achievable concentrations of idebenone are sufficient for this mechanism of action (MOA) to occur.

In view of the hypothesized involvement of mitochondrial dysfunction, and particularly the reduced activity of the ETC, idebenone is a rational treatment choice in PP-MS based on its pharmacological properties. Furthermore, idebenone is known to cross the blood-brain barrier *(Torii, Yoshida et al. 1985)* and is readily taken up by cells, even those with normal CoQ_{10} content *(Geromel, Darin et al. 2002)*, making it superior to natural CoQ_{10} for treatment of CNS diseases with presumed mitochondrial dysfunction.

There are several secondary effects of idebenone described in the literature, which may be useful from the standpoint of the presumed pathophysiology of PP-MS:

3) Animal studies have documented neuroprotective properties of idebenone *in-vitro* in different models of excitotoxicity (by NMDA and kainite-agonists) *(Miyamoto and Coyle 1990; Bruno, Battaglia et al. 1994)*.
4) Idebenone induces nerve growth factor expression in animals *(Nitta, Murakami et al. 1994)*, which represented the basis for its presumed neuroprotective effect in Alzheimer's disease (AD) *(Gutzmann and Hadler 1998; Gutzmann, Kuhl et al. 2002)*. However, this beneficial effect on AD is only very mild and perhaps not highly clinically relevant *(Thal, Grundman et al. 2003)*.
5) Idebenone has potential CNS anti-inflammatory activity, as it inhibits metabolism of arachidonic acid by cyclooxygenase and lipoxygenase *(Civenni, Bezzi et al. 1999)*.
6) Idebenone may substitute for CoQ_{10} in non-mitochondrial locations such as in lysosomes, peroxisomes and plasma membranes, protecting these organelles from ROS-associated damage *(Geromel, Darin et al. 2002)*

Due to its effect as a scavenger of oxygen radicals and facilitating effect on ETC, idebenone has been used extensively with reported success in patients with mitochondrial diseases *(Mashima, Hiida et al. 1992; Ikejiri, Mori et al. 1996; Napolitano, Salvetti et al. 2000; Lerman-Sagie, Rustin et al. 2001; Geromel, Darin et al. 2002)*. As mentioned above, the first randomized trial of idebenone in LHON demonstrated improvements of vision in the active therapy arm in comparison to placebo, although statistical significance was obtained only for secondary outcomes *(Klopstock, Yu-Wai-Man et al. 2011)*. LHON is the most common mitochondrial disorder, causing progressive loss of vision. Pathogenic mutations of mtDNA, which affect ETC complex I, lead to decreased ATP synthesis accompanied by increased mitochondrial production of ROS. Painless loss of vision on one eye, which usually occurs in early adulthood, is followed by progressive irreversible blindness of the second eye usually within 3 months. Idebenone not only significantly inhibited the worsening of eyesight in the less affected eye in patients with discordant visual acuities, but also caused general improvement in all visual outcomes (i.e. including in the eyes that were chronically blind), although

this improvement did not reach statistical significance for the primary outcome, which was best recovery of visual acuity considering both eyes *(Klopstock, Yu-Wai-Man et al. 2011).* These objective improvements of visual function in the intention to treat analysis correlated with the patients' global impression of change. In the group of patients who could not read any letters on the vision chart at baseline, 20% of the eyes of the patients receiving idebenone were able to read at least one full line on the chart at week 24, while none of the patients in the placebo group showed such improvements (p=0.008). Additionally, idebenone treatment caused significant improvements in color contrast sensitivity (by 13.63-14.51%, p=0.004). These functional data were supported by OCT data that demonstrated a trend toward maintaining retinal nerve fiber thickness in the idebenone group *(Klopstock, Yu-Wai-Man et al. 2011).*

We consider the data from LHON highly relevant for MS because of the known association between LHON and MS, called Harding's syndrome *(Vanopdenbosch, Dubois et al. 2000).* It appears that carrying a primary LHON mutation dramatically increases the risk for development of MS: Harding's syndrome occurs 50 times more frequently than would be expected from the individual prevalence rates for LHON and MS *(Palace 2009; Stys, Zamponi et al. 2012).* As we described above, demyelination causes secondary mtDNA mutations and functional defects in ETC complex I that are pathophysiologically similar to inborn genetic errors associated with LHON.

There was also a therapeutic benefit of idebenone observed in Phase II trials in the neurodegenerative disease Friedreich's ataxia (FRDA), which unfortunately did not reach statistical significance in the confirmatory Phase III trial *(Meier, Perlman et al. 2012)*. FRDA is the most common hereditary ataxia inherited as an autosomal recessive GAA expansion in the first intron of the frataxin gene. Frataxin is a nuclear encoded protein, which is exported to the mitochondria. Frataxin plays an important role in the assembly of mitochondrial FE/S clusters that are key components of the ETC. Its decreased expression therefore leads to reduced activity of the ETC, mitochondrial damage with subsequent increased formation of reactive oxygen species (ROS). It was demonstrated that FRDA has reduced ATP biosynthesis. The reduced activity of the ETC in combination with secondary oxidative damage is believed to underlie the development of neurological disability and hypertrophic cardiomyopathy and diabetes, which are characteristic clinical presentations of this disease. Idebenone has been studied extensively in FRDA *(Schols, Vorgerd et al. 2001; Artuch, Aracil et al. 2002; Rustin, Rotig et al. 2002; Buyse, Mertens et al. 2003; Mariotti, Solari et al. 2003; Artuch, Aracil et al. 2004; Rustin, Bonnet et al. 2004; Di Prospero, Baker et al. 2007; Pineda, Arpa et al. 2008)*, including successful studies performed at intramural NIH by the Neurogenetics Branch research group under the leadership of Dr. Kenneth Fischbeck *(Di Prospero, Baker et al. 2007)* in collaboration with Santhera. This study demonstrated that intermediate to high (10-50mg/kg) doses of idebenone were effective in slowing the progression of disability in FA patients as compared to low dose idebenone (4-8mg/kg) and placebo. Because previous trials using lower doses of idebenone in FRDA demonstrated a positive effect on cardiac function but not on neurological function *(Mariotti, Solari et al. 2003)*, it is likely that higher doses of idebenone are necessary for penetration into the CNS. This conclusion is fully supported by above-mentioned Phase III trial (IONIA) that studied two weight-adjusted doses of idebenone: low dose (450/900mg) or high dose 1350/2250mg) and its open label extension (IONIA-E), where patients who received the higher dose of idebenone (1350/2250mg) for 18 months significantly improved in neurological function *(Meier, Perlman et al. 2012).*

In conclusion, the three major effects of idebenone (facilitating ETC mitochondrial function, antioxidant/scavenger of ROS and potentially also anti-inflammatory) make it an excellent candidate agent for the treatment of PP-MS based on the neurodegenerative hypothesis described above. Additionally, idebenone is an oral therapy with extensive safety and tolerability data.

4.7 Rationale for current study design

The clinical experience with use of antioxidants in MS is very limited: although a few trials of antioxidants in MS have been reported *(Jensen and Clausen 1986; Spitsin, Hooper et al. 2001; Yadav, Marracci et al. 2005)*, all have been small studies of short duration and offered only very limited insight on clinical efficacy *(Spitsin, Hooper et al. 2001)*.

Idebenone is currently being used in a proof-of-principle placebo-controlled, Phase I/II clinical trial for PP-MS (IPPoMS trial; Protocol Number 09-N-0197). Patients who have completed the 2 year treatment period of the IPPoMS study will be given the opportunity to enter the current open-label extension (IPPoMS-E) study. The IPPoMS study stipulates, in accordance with FDA Good Clinical Practice (GCP) recommendations, that the blind will be broken only after all study subjects have completed all study visits and all outcomes have been logged into the database. Therefore, patients will have to decide whether they want to participate in the IPPoMS-E study without having knowledge about their assignment to idebenone versus placebo group during IPPoMS trial. This could cause an ethical dilemma for patients who might have been in the idebenone arm during the IPPoMS trial and did not experience satisfactory therapeutic response, because the option to participate in IPPoMS-E would theoretically prevent them from pursuing other therapeutic options. However, because there are currently no effective therapies for PP-MS, we deem this theoretical problem not applicable to IPPoMS-E trial.

The IPPoMS-E population will comprise both patients randomized to idebenone or to placebo in the IPPoMS study. Therefore all safety and efficacy assessments conducted for the IPPoMS study will also be conducted for the IPPoMS-E (Figure 2). This is particularly important for patients randomized to placebo in IPPoMS now receiving idebenone for the first time in IPPoMS-E.

The aim of the present study is extend the data on safety, efficacy and effects on CSF biomarkers of idebenone 2250mg/day (5x150mg tablets three times per day) in patients with PP-MS, over a period of 1 year. Considering the dynamics of improvements in neurological function observed in double blind placebo-controlled trial of idebenone in LHON *(Klopstock, Yu-Wai-Man et al. 2011*) and in FRDA *(Di Prospero, Baker et al. 2007)* we believe that if there was a meaningful therapeutic effect of idebenone in PP-MS, then one year of active therapy would provide sufficient time to observe a difference in the rate of accumulation of neurological disability as compared to the 3 years of natural history from the IPPoMS placebo arm. IPPoMS-E will also provide safety and efficacy data for an additional 1 year in patients randomized to idebenone in IPPoMS.

Furthermore, the IPPoMS-E study will significantly expand the amount of longitudinal CSF biomarker data for idebenone-exposed PP-MS subjects. In patients randomized originally to active drug, IPPoMS-E study will effectively provide three yearly CSF samples on idebenone therapy. Such longitudinal CSF biomarker data on active therapy can be then compared to longitudinal CSF

biomarker data off therapy (i.e. 3 yearly CSF samples in the original placebo arm) for mathematical modeling studies that may provide support for, or contest, a potential neuroprotective effect of idebenone in PP-MS (see section 11: Statistical analysis). Furthermore, the number of paired CSF samples before and after idebenone therapy may theoretically increase up to 100% (if all patients choose to continue in IPPoMS-E protocol), although we consider it likely that some patient will decline participation in IPPoMS-E. This expansion of paired baseline versus treatment CSF samples will effective provide confirmatory cohort for validation of the changes induced by idebenone treatment that were defined in original IPPoMS trial (see section 11: Statistical analysis).

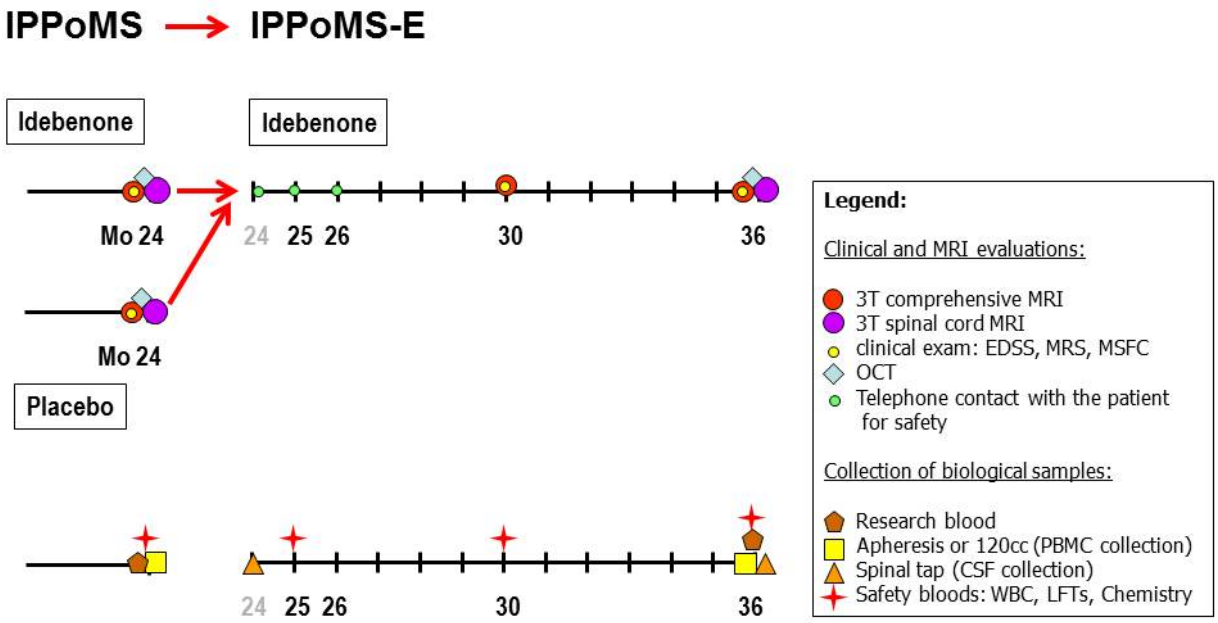

Figure 2: IPPoMS-E trial design

We believe that expansion of efficacy on clinical, imaging and biomarker data may be highly important for supporting or refuting presumed therapeutic equipoise of idebenone and placebo in PP-MS and for selecting the optimal patient population and optimal trial design for the confirmatory trial in case IPPoMS and IPPoMS-E trials indicate therapeutic efficacy.

5. STUDY OBJECTIVES OR HYPOTHESES

5.1 Hypothesis

We hypothesize that idebenone, through its combined effect on facilitation of mitochondrial metabolism and limitation of oxygen radical-induced CNS damage, will inhibit CNS tissue destruction in PP-MS patients.

5.2 Goals of the study

The primary goals are:

1. To extend long-term (36 months) data on the safety and tolerability of idebenone at 2250 mg/day in patients with PP-MS.
2. To extend CSF biomarker data by significantly expanding (up to 2 fold if all eligible patients proceed to IPPOMS-E) the matched "baseline" vs. "idebenone treatment" CSF samples, which will be analyzed for biomarkers of oxidative stress, mitochondrial function and CNS tissue integrity.
3. To extend efficacy data for idebenone on CNS tissue destruction as measured by quantitative imaging biomarkers and clinical/functional biomarkers in patients previously completing IPPoMS (Protocol Number 09-N-0197). For patients originally randomized to active drug, the idebenone longitudinal data will be extended for total of 3 years, for patients originally randomized to placebo, 3 year pre-treatment or placebo-treatment period will be compared to 1 year idebenone therapy period.

The secondary goals are:

1. To further investigate the mechanism of action of idebenone in PP-MS.
2. To better define biomarkers indicative of therapeutic effect of idebenone on mitochondrial dysfunction and on limiting oxidative damage in PP-MS patients.

6. SUBJECTS

6.1. Study population

Eligible patients completing the IPPoMS trial will be offered the opportunity to enroll in this IPPoMS-E study.

It is important that no break in study medication between the IPPoMS randomized phase and the present study occurs. Such a break in therapy will render interpretation of study outcomes in this trial more difficult. However, if a patient does finish the IPPoMS randomization phase before this IPPoMS-E study is approved for use, they will be allowed to enter the IPPoMS-E trial.

6.2. Inclusion criteria

1. Completion of 3 years in study IPPoMS (Protocol Number 09-N-0197)
2. Able to provide informed consent
3. Adults, at least 18 years of age.
4. Willing to participate in all aspects of trial design and follow-up

5. If able to become pregnant or to father a child, agreeing to commit to the use of a reliable/accepted method of birth control (i.e. hormonal contraception (birth control pills, injected hormones, vaginal ring), intrauterine device, barrier methods with spermicide (diaphragm with spermicide, condom with spermicide) or surgical sterilization (hysterectomy, tubal ligation, or vasectomy)) for the duration of treatment arm of the study

6.3. Exclusion criteria

1. Pregnant or lactating women. All women of child-bearing potential must have a negative pregnancy test
2. Patients dropping out of IPPoMS due to AEs considered related to study medication

7. STUDY DESIGN AND METHODS

7.1 Study overview

This is a Phase II open-label trial of the safety and efficacy of idebenone at 2250 mg/day with one year treatment period. Patient-specific biomarkers of disease progression and longitudinal neuroimaging and clinical data will be collected as for the randomized study.

7.2 Recruitment

Eligible patients completing the IPPoMS (Protocol Number 09-N-0197) will be offered the opportunity to enroll in this open-label extension study IPPoMS-E.

7.3 Screening methods

Not applicable.

7.4 Study design

Patients will be given idebenone (2250 mg/day, given as five 150 mg tablets, three times a day) and will be followed by combined neurological, neuroimaging and research biomarker/immunological evaluations every 6 months for 1 year. In addition, patients will have safety labs drawn at month 25 which can be drawn at NIH or at an outside lab with results (including normal values) communicated to NIH investigators. Telephone interviews will occur 1 week, 1 month (Mo 25) and 2 months (Mo 26) after initiation of dosing. Patient's safety and change in neurological function will be assessed during the telephone interview with an investigator (Figure 2).

The IPPoMS-E Baseline information will be provided by the results of the IPPoMS Month 24 assessments.

The time commitment will include extension of the last visit on IPPoMS trial (which will serve as initial visit in IPPoMS-E trial) and 2 additional prolonged outpatient or inpatient visits in the 1 year

period. Each prolonged visit will have procedures that together last at least 8 hours spread over 1-3 days.

According to negotiated MCRADA, Santhera Inc. will supply sufficient amount of idebenone for completion of the proposed trial (i.e. 1 year dosing for up to 85 patients). There is no negotiated provision for Santhera to continue to provide drug on a compassionate basis for any of the patients after completion of the trial.

7.5 Study procedures

7.5.1 Study visits

The last study visit in IPPoMS will serve as the baseline visit for this extension study, at which time informed consent will be obtained and patient will undergo the first lumbar puncture and associated research bloodwork under IPPoMS-E protocol. Each subsequent IPPoMS-E study visit (Figure 2) and MRI should occur as indicated. These time points are approximated. To accommodate for patient scheduling needs or clinical necessity, study visits will be accepted within a +/- 4 week window of the time points noted. Biological samples (CSF, whole blood or apheresis sample) should be collected within 4 weeks of the MRI examination as indicated in Figure 2. Blood samples at the IPPoMS mo 24 visit and 36 month IPPoMS-E will be collected concomitantly with CSF samples in the IPPoMS-E trial.

Because most patients enrolled in IPPoMS trial do not live locally, their clinical visits will be associated with travel to NIH for either inpatient or outpatient visits lasting 1-3 days. During these extended visits all study procedures pertaining to a specific study time point will be performed. We estimate that the total duration of all study procedures pertaining to a single study timepoint is 8-12 hours.

7.5.2 Clinical and functional evaluations:

1. Comprehensive neurological evaluation
2. Expanded Disability Status Scale (EDSS *(Kurtzke 1983)*)
3. Scripps Neurological Rating Scale (NRS *(Sharrack and Hughes 1996)*)
4. MS Functional Composite Scale (MSFC *(Cutter, Baier et al. 1999)*, which consists of 3 functional tests:
    a. Paced Auditory Single Digit Addition Test (PASAT) – measure of cognitive skills
    b. Timed 25 foot walk – measure of ambulation
    c. 9-hole peg test – measure of fine finger motor movements
5. Symbol Digit Modality Test *(Sepulcre, Vanotti et al. 2006)*
6. Extensive evaluation of strength, balance and gait within the context of a physical therapy (PT) evaluation will be performed if the subject is not too disabled to participate in these evaluations safely and reliably. This optional evaluation will be conducted in the Biomechanics Laboratory of the Rehabilitation Medicine Department, NIH, CC. It will include, but may not be limited to, the following:
    a. Evaluation of strength and tone
    b. Evaluation of gait

c. Balance assessment

7.5.3 Neuroimaging evaluation:

MRI imaging will consist of:

1) MRI of the brain, which will be performed every 6 months. This MRI will focus on quantitative and volumetric analyses of brain structure and tissue integrity. Inflammatory activity is less prominent in PP-MS as compared to RR-MS and consequently, the vast majority of PP-MS patients do not have evidence of gross blood-brain barrier (BBB) disruption as measured by contrast-enhancing lesions (CEL). Therefore, gadolinium (Gd) may not be administered during every scan. Clinical judgment will determine if Gd is administered during the remaining 3T brain MRI scans. The total scan time without Gd administration is approximately 90 minutes. With Gd, the scan time increases to 2 hours.

2) MRI of the spinal cord. This will focus on analysis of spinal cord volume and detection of lesions. We will investigate the feasibility and value of quantitative spinal cord structural integrity measures as well. This scan will be performed at Mo 30 and Gd administration will be based on clinical judgment. The total scan time is approximately 75 minutes without Gd and 90 minutes with Gd.

7.5.4 Optical coherence tomography (OCT)

OCT will be performed at the conclusion of IPPoMS-E trial. OCT is a new noninvasive high-resolution method that measures the retinal nerve fiber layer (RNFL) thickness. It works by measuring the echo time delay and intensity of back-reflection of light from different structures in the eye. Recent studies have shown that OCT can detect RNFL thinning, possibly due to axon degeneration, within the retinas of patients with MS, regardless of a clinical history of optic neuritis *(Kallenbach and Frederiksen 2007)*. Moreover, RNFL thickness appears associated with global brain atrophy, (manifested by increasing CSF volume) (Gordon-Lipkin, Chodkowski et al. 2007). As discussed, reliable methods of measurement of neurodegeneration in MS are lacking. While a more thorough characterization is needed, evidence to date suggests that OCT may be developed as a novel measure of neuronal/axonal destruction reflective of neurodegeneration in MS with both diagnostic and prognostic potential *(Gordon-Lipkin, Chodkowski et al. 2007; Kallenbach and Frederiksen 2007)*.

7.5.5 Transcranial magnetic stimulation (TMS) and Central motor conduction time (CMCT) calculation

TMS and CMCT may be performed for clinical care.

Neurophysiological testing, can assess the intactness of conduction through the long tracts, such as the corticospinal tract (CST) *(Ravnborg 1996)*. Because CST is invariably affected in PP-MS, the use of motor evoked potentials (MEP) may be performed for clinical care. TMS is a non-invasive technique for evaluating the function of central motor pathways. Single pulse TMS is used to determine the motor evoked potential (MEP), the response generated by excitation of cortical neurons and recorded at the target muscle, and is used to calculate the central motor conduction time

(CMCT). In MS patients, CNS dysfunction manifests itself in the form of slowed conduction through demyelinated portions of the corticospinal tracts or more severe disruption of conduction as a result of axonal loss or severe demyelination. This results in a prolongation of CMCT or dispersion of the MEP response such as in a conduction block with resultant decrease in MEP amplitude *(Hess, Mills et al. 1987; Schriefer, Hess et al. 1989)*. In progressive MS patients, CMCT has been shown to correlate with the presence of new spinal cord lesions on MRI and changes in the leg CMCT *(Kidd, Thompson et al. 1998)*. There is other evidence that suggests that progressive MS patients have greater prolongation of the CMCT compared to relapsing-remitting MS, irrespective of MRI lesion load, suggesting that progressive MS has more perturbations of the corticospinal tracts than are radiologically discernible *(Humm, Z'Graggen et al. 2004)*.

7.5.6 Immunological and laboratory evaluation:

The immunological and laboratory evaluation will include:

1. Clinical blood-work (clinical care/safety): CBC, Chemistry panel including liver function tests will be performed one month after initiation of open label dosing (Mo 25), Mo 30, and Mo 36. Laboratory evaluations that are performed at times when no NIH MRI/clinical visit is scheduled (Mo 25) can be performed outside of NIH with results (including normal values) communicated to NIH investigators. PT/PTT and PFA panel may be collected as additional safety measures at month 30 and 36. Urine analysis (UA) will be performed every 6 months. Pregnancy tests (for females of child-bearing potential) will be collected up to 24h preceding every MRI exam. All safety laboratory evaluations are represented in the clinical trial scheme on Figure 2.
2. Research Blood (up to 40 cc total): Research blood will be obtained concomitantly with the LP Lumbar puncture (research): Every patient will undergo a lumbar puncture at the beginning of IPPoMS-E trial (month 24) and after 1 year of therapy (month 36). This procedure is performed solely for research purposes. From 15-20cc of research specimen, immune cells will be isolated and expanded and the CSF supernatant will be aliquoted and stored. In certain cases (generally with participants who are obese, who have limited mobility, or who have lumbar spondylosis), the procedure may be performed under fluoroscopic guidance by a credentialed neuroradiologist in Diagnostic Radiology. This involves a small amount of ionizing radiation (0.023 rem per year). This is substantially less than the limits imposed by the guidelines of the NIH Radiation Safety Committee (5.0 rem per year for adults).
3. Lumbar puncture procedure last from 30 minutes to 2 hours.
4. Pharmacokinetic (PK) studies (research): Random sampling PK studies may be performed from the CSF at the time of LP, for the analysis of IDE and IDE+IDE-C and the metabolites QS-10, QS-6 and QS-4, as well as QS10+QS10-C, QS6+QS6-C and QS4+QS4-C. Samples will be put on ice immediately and centrifuged at 4°C at 1500 g for 10 minutes within 30 minutes after sampling. The cell-free aliquots will be separated and stored separately in polypropylene tubes with a minimum of 0.5ml of CSF per tube. Samples will be stored between -70 and -80°C. The CSF will be collected for possible future PK studies to be performed by Santhera Pharmaceuticals upon completion of the collection of all trial samples, using a validated LC-MS/MS method (Inovalab, Reinach, Switzerland)
5. Lymphocytapheresis (research): collecting between 2-4x10^9 peripheral blood mononuclear cells PBMC, will be performed after 1 year of idebenone therapy (Mo 36). This procedure is performed solely for research purposes. This procedure may last up to 2.5 hours. If the

participant is unable to undergo lymphocytapheresis for any reason, 120 cc of whole blood in a heparinized syringe will be collected in its place. The collected mononuclear cells will be used for immunological studies.

7.5.7 Drug administration:

A copy of this protocol has been submitted to the FDA under the existing IND for review. Santhera provided a letter of cross-reference to the IND held by them.

Idebenone (150mg tablets) will be administered orally as five tablets, three times per day with food. Patients will receive a 6 month supply of the study medication. Patients will record drug administration in a drug diary. Remaining pills and bottles will be counted during clinic visits every 6 months to assess overall drug compliance.

Idebenone is a short-chain benzoquinone derivative of similar structure to ubiquinone (coenzyme Q_{10}). This compound was synthesized and developed initially by Takeda Chemical Industries, Ltd. (Osaka, Japan) and designated as CV-2619. The chemical name for idebenone is 6-(10-Hydroxydecyl)-2,3-dimethoxy-5-methyl-1, 4-benzoquinone. Santhera Pharmaceuticals (Switzerland) Ltd, will supply the drug for this study as specified by a clinical trial agreement. Idebenone is formulated as film-coated 150 mg tablets. For list of inactive ingredients see section 4.5.4.

Idebenone with a certificate documenting analytical results, release of the product for the clinical study and shelf life will be provided to the NINDS by Santhera Pharmaceuticals (Switzerland) Ltd. Idebenone tablets are supplied in high density polyethylene (HDPE) bottles, should be stored at room temperature (15-25ºC) and must be protected from direct sunlight. Temperature excursions are permitted as follows: up to 30ºC for 12 months, up to 40ºC for 6 months.

7.5.8 Records:

The NINDS/Clinical center record will be used for trial-related documentation. Specific trial-related pages will include:

Inclusion and exclusion criteria checklist
Documentation of the history and physical examination (using structured NIB progress note)

1. A copy of the written informed consent.
2. A record of all research tests, scores, and results.
3. Documentation of all clinical laboratory results.
4. Documentation of any concomitant medications taken by the patient.
5. A record of any and all adverse events experienced during the study.

7.5.9 Storage of data and samples:

All collected samples, including serum/plasma, blood, CSF and peripheral blood mononuclear cells (PBMC) derived from apheresis or 120cc blood sample (see 7.5.6) will be coded and stored in secured freezers on the NIH campus. All patients enrolled in this protocol will be assigned a

sequential code and all biological samples collected for this patient will be labeled with patient's code, type of the sample, volume, number of cells (if indicated) and date of freezing.

The intent is for all samples (except for those to be analyzed for idebenone and metabolite pharmacokinetics) to be analyzed in laboratories on the NIH campus. As new relevant methodologies are developed, however, there is a conceivable future interest to process samples off-site in a collaborating laboratory. Patients will be made aware of this possibility at the time of enrollment and will be asked to consent to potential off-site processing. In this event, IRB approval from NIH and from the collaborating institution will be obtained, and materials will be shipped in accordance with NIH and federal regulations.

7.6 Follow-up/termination procedures

The individual participation in the trial will end with the last trial visit at month 36, unless the trial is closed prematurely. There will be a telephone interview 1 month after completion of the trial to verify that there has been no worsening of the clinical symptoms. In case of serious adverse events ongoing at the last trial visit (month 36) **or** of SAEs newly reported during the telephone contact, the patient will be invited to undergo a full examination and assessment at the study site. Additionally, patients will be asked to report any serious adverse event that may occur after this last interview, if they perceive them as possibly related to the participation in this study. The trial will be officially terminated after all enrolled subjects complete the telephone visit (month 37) or withdraw from the trial. The trial may be terminated prematurely by the DSMB if there is a concern about safety of idebenone in PP-MS patients.

All clinical data will be prospectively acquired and entered into the NIB research database. Similarly, all neuroimaging volumetric data will be transcribed into the NIB research database. All immunological and/or biomarker data will be logged and stored in a separate research database on the NINDS server. In order to limit inter-assay variability, for those biomarkers that can be measured from cryopreserved biological samples, all time-points for individual research subjects will be run in parallel. All databases will be locked upon the last entry of data from the last patient who completes the trial.

7.6.1 Premature trial termination for futility - patient follow-up

As of this protocol amendment, the IPPoMS study 09-N-0197 (Blinded parent study of idebenone vs placebo) has completed analysis and demonstrated that idebenone, while being safe and well-tolerated, had no significant efficacy on either primary or any secondary outcome measures, in comparison to placebo. As a result, this open-label extension study will be stopped for futility. No additional patients will be enrolled onto this protocol. All participants are co-enrolled into natural history study 09-N-0032, and may continue follow-up under that study. Data and samples from this study will be transferred into protocol 09-N-0032 for continued analysis. Participants will be contacted by phone and formally informed of the study results by a written letter (uploaded to PTMS). Participants will return for a final study visit, and any remaining study drug will be collected. The final study visit will include the following procedures: clinical evaluation, MRI and safety lab work.

8. RISKS/DISCOMFORTS

8.1 Risks associated with Idebenone therapy

There is considerable clinical trial and post-marketing experience indicating that idebenone is well tolerated and has a good safety profile. Safety data are available from 311 patients with Friedreich's Ataxia (FRDA) or Leber Hereditary optic neuropathy (LHON) treated with idebenone at doses of between 900 and 2250 mg/day. No noteworthy imbalances in the distribution of adverse events (AEs) were observed for the comparison of idebenone or placebo. The most commonly observed adverse reactions were gastrointestinal disorders. The following reactions were observed in more than one patient: headache, diarrhea, nausea and dyspepsia. The following reactions were not observed in more than one patient at the recommended doses: white blood cell count decrease, disturbance in attention, angina pectoris, vomiting, reflux oesophagitis, musculoskeletal chest pain, myalgia, upper abdominal pain.

Clinical trials with idebenone have previously been performed in indications other than FRDA and LHON, predominantly in older patient populations (mainly in Alzheimer's dementia). Besides some of the reactions listed above, patients in these trials showed the following reactions uncommonly (between 1/1000 and 1/100): sleep disorders, nervousness, dizziness, changes in hepatic laboratory values and influenza-like symptoms. These reactions may be more likely in this elderly study population with CNS impairment and more concomitant medications.

The IPPoMS trial will randomize up to 85 PP-MS patients either to idebenone (2250 mg/day) or to placebo. This study is under the supervision of a Data Safety Monitoring Board. By July 2012 approximately 20 patients had been treated with study medication. Five Serious Adverse Events (SAEs) have been reported on this trial to date but all were considered unrelated to study medication and the DSMB had raised no safety concerns with regard to the conduct of the study.

Idebenone at high doses (60-75 mg/kg/day or about 3600-4500 mg/day) may cause orange discoloration of urine in few patients. It is unclear if this will occur at the dose of 2250mg/day. The orange discoloration of urine is completely harmless and urine will be monitored every 6 months by urinalysis in order to ensure that hematuria or hemoglobinuria is not mistaken for the orange discoloration due to idebenone.

8.2 Risks of lymphocytapheresis

Adverse reactions associated with lymphocytapheresis include vasovagal syncope with needle insertion and rare hypotension secondary to volume depletion. Because of the controlled nature of these procedures hypotension is unlikely. Exclusion of patients with a history of cardiovascular disease further reduces the risk of this complication. The blood thinner used to prevent blood clots from apheresis can cause mild muscle cramps. If these side effects occur, we can slow down blood flow or use a different blood thinner. If the symptoms do not go away, the apheresis can be stopped. There may also be bruising at the site of needle insertion. Infection is a potential risk, but is unlikely

due to the closed system and the maintenance of sterile technique. The Blood Bank has extensive experience with these procedures and has encountered no serious side effects.

8.3 Risks of MRI

People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner or tattoos, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye, of which they may be unaware. All subjects will be screened for these conditions prior to the study, and if they have any, they will not receive an MRI scan.

Gadolinium is a contrast agent approved for use with MRI by the FDA. No serious side effects have been associated with its use. The effect of gadolinium on the developing fetus remains partly unknown. Animal studies have shown a delay in development but no developmental abnormalities. Consequently, women of childbearing potential will be entered into this study only if an effective means of birth control is in use. A pregnancy test will be done prior to beginning the study and pregnancy tests will be done before MRIs are performed. The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling. Symptoms from the contrast infusion are usually mild and may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number of patients, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. Subjects should not receive gadolinium-based contrast agents if they have previously had an allergic reaction to them. Subjects will be asked about such allergic reactions before a contrast agent is administered. People with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis” which has resulted in a very small number of deaths. If patients are older than 60 or have diabetes, kidney disease or liver disease, bloodwork to assess kidney function will be performed within 4 weeks before any MRI scan with gadolinium contrast. Patients may not receive gadolinium for a research MRI scan if kidney function is not normal. The long term effect of noise exposure from MRI is not known.

8.4 Risks of lumbar puncture

Adverse effects associated with lumbar punctures include brief pain or tingling paresthesias radiating down the lower extremity due to the needle brushing against a nerve. Should this occur, the needle can be repositioned. Mild lower back pain at the site of needle insertion following the procedure can occur; this can be managed with over the counter non-steroidal anti-inflammatory agents if needed. In approximately one third of patients, a post-dural puncture headache may develop and persist for a few days; in one in 50 to 200 lumbar punctures the post-dural puncture headache can last longer than 7 days. Generally this headache is not severe and resolves spontaneously within days - 2 weeks. Should the headache persist or be severe, a blood patch can be performed. An extremely rare complication of lumbar puncture includes temporary double vision related to abducens nerve palsy, and infection. Strict aseptic technique will be followed. Collecting additional 10-15 cc of CSF per procedure represents negligible risk (Evans, Armon et al. 2000). In humans the rate of CSF synthesis is approximately 21.5 cc/hour (Kimelberg 2004), or approximately 500cc/24hours, which represents

roughly 4 times the total volume of CSF in an adult patients. Therefore, the volume of 20-30cc of CSF that would be collected for both diagnostic and research purposes will be replenished in its entirety within approximately 1-1.5 hours after collection. Lumbar puncture may be done in the radiology department under fluoroscopic guidance for patient medical or scheduling needs. The radiation exposure during this procedure is 0.023 rem, which is well below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

8.5 Risk of OCT

There are no known medical risks of optical coherence tomography.

8.6 Risk of electrophysiological studies

8.6.1 Risk of TMS

TMS is a safe procedure that has been used on thousands of people throughout the world, particularly the single-pulse TMS used in this study. Most people do not find the stimulation painful, but sometimes strong contractions of scalp muscles can cause discomfort or headache. Headaches usually go away promptly with nonprescription medication. The noise of the TMS magnet may damage hearing; therefore the subjects will be fitted with earplugs that must be worn during TMS. TMS can interfere with implanted medical devices and will not be done in people who have pacemakers, implanted pumps, or stimulators, such as cochlear implants or in people who have metal objects inside the eye or skull.

8.6.2 Risk of nerve conduction studies

The risks of the electrical stimulation using commercial isolated stimulators are low. Most subjects find electrical nerve shocks to be mildly uncomfortable; it is usually perceived as a brief stinging or tapping sensation. The intensities required for nerve conduction studies are usually well tolerated.

8.7 Risk Rehab Evaluation

The risk of physical injury in this series of noninvasive tests is minimal.

9. SUBJECT MONITORING

9.1 Parameters to be monitored

9.1.1 Expected Adverse Events:

Animal studies predict a low human toxicity profile for idebenone. This is supported by extensive experience including phase I trials in normal human volunteers and phase II and III trials in patients with Alzheimer's disease, FRDA, LHON, Duchene Muscular Dystrophy (DMD), cerebrovascular accident (stroke), multi-infarct dementia, and other neurodegenerative diseases (e.g. Huntington's disease), at doses comparable to those being used in this study. Based on the literature review of published data from these studies, the most frequently and consistently experienced adverse

reactions reported across these trials have been headache, diarrhea, nausea and dyspepsia. A complete list of previous adverse events, which may also be expected in this trial, may be found in the Investigator's Brochure and is summarized in section 7 of that document. In addition, medical events typical for clinical course of PP-MS (i.e. typical neurological signs/symptoms that patient experienced during pre-treatment baseline and their worsening as would be expected from the natural history of PP-MS) can be regarded as expected events in the course of the current trial.

9.1.2 Monitoring of adverse events:

The patient will be instructed to contact the investigator immediately should the patient manifest any sign or symptom perceived as serious during the period extending from performance of the first study procedure (e.g. drawing of a blood sample) up to and including 1 month after the last dose (telephone interview at month 37). After this period of time, the patient should report to the investigator only adverse events that are serious and perceived as possibly related to their participation in this study. Additionally, the patient will be instructed to contact the investigator immediately if he/she believes that he/she has fathered/conceived a child. Testing would be performed to verify that the subject or subject's partner was pregnant. If the pregnancy test were positive, the patient would be instructed to immediately stop taking the study drug. The patient or partner would be counseled and followed closely during the pregnancy by the NIH research team and would implement any recommendations made by the DSMB.

Patients will be physically examined by the investigator approximately every 6 months for the study duration. One week, one month (Mo 25) and 2 months (Mo 26) after initiation of dosing, patient's safety and change in neurological function will be assessed by telephone interview with an investigator (Figure 2).

Extensive laboratory monitoring (CBC with differential and Chemistry panel 20, which includes LFTs) will occur three times during the study duration: at month 25, 30, and 36 (Figure 2). Urinalysis and pregnancy test (for females with childbearing potential) will be performed every 6 months (before MRI).

All adverse events occurring within 1 month following the last administration of the study medication must be recorded on the Adverse Event Form irrespective of severity and seriousness, and whether or not they are considered related to the study medication. Additionally, all serious adverse events (SAE) brought to the attention of the investigator during the period starting from the day of performance of the first study procedure to the telephone interview on month 37, must be recorded and reported to the FDA in accordance with federal regulations and NIH procedures. Any SAE reported by the patient after month 37, will be subjected to expedited reporting only if judged to be related to the study treatment by the Investigator.

The collection of complete and accurate information is of paramount importance to allow a full evaluation of SAEs. Each SAE will be properly documented and followed up until the event is resolved, subsided, stabilized, disappeared or is otherwise explained or the study patient is lost to follow-up. Recurrent episodes, complications, or progression of the initial SAE will be reported as follow-up to the original episode, regardless of when the event occurs. Follow-up of reportable SAEs will be submitted to the FDA, IRB and Santhera Pharmaceuticals (Switzerland) Ltd. according to the

same timelines mandatory for initial reports, i.e. within 7 calendar days for fatal/life-threatening and 15 calendar days for all other SAE. An SAE that is considered completely unrelated to one previously reported, will be reported separately as a new event.

When a Serious Adverse Drug Reaction occurs during the clinical trial, the NINDS will provide Santhera Pharmaceuticals (Switzerland) Ltd. or designee with: a) primary safety information (i.e. short description including at least patient's study number, age and gender; reported SAE terms and causality assessment) at the time when the NINDS clinical director and the head of IRB are informed and no later than by Day 4; and b) copies of all Serious Adverse Drug Reaction reports concurrently with their submission to the FDA, including copies of any warning letters or other information affecting the safety and/or well-being of human subjects in research conducted under this MCRADA.

9.2 Toxicity tables/criteria to be used

Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Publish date August 9, 2006). A copy of the Common Terminology Criteria for Adverse Events version 3.0 can be downloaded from http://ctep.cancer.gov/reporting/ctc_v30.html.

9.2.1 Definition of Adverse Event (AE)

An AE is "*any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen*." An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

9.2.2 Severity of Adverse events

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild AE
Grade 2 Moderate AE
Grade 3 Severe AE
Grade 4 Life-threatening or disabling AE (SAE)
Grade 5 Death related to AE (SAE)

Assessment	Definition
1 = Mild	Discomfort noted, but no disruption of normal daily activities; slightly bothersome; relieved with or without symptomatic treatment
2 = Moderate	Discomfort sufficient to reduce or affect normal daily activity to some degree; bothersome; interferes with activities, only partially relieved with symptomatic treatment.
3 = Severe	Discomfort sufficient to reduce or affect normal daily activity considerably; prevents regular activities; not relieved with symptomatic treatment.

9.2.3 Definition of Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence or effect at any dose, that:

- results in death,
- is life threatening,
- results in persistent or significant disability/incapacity,
- requires in-patient hospitalization‡ or prolongation of existing hospitalization,
- results in cancer,
- is a congenital anomaly/birth defect in the offspring of a study subject,
- is deemed, by the investigator, an important or serious medical event that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious (i.e., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.)

9.2.4 Assessment of causality

Every effort should be made by the investigator to explain each adverse event and assess its causal relationship, if any, to the study medication. The degree of certainty with which an adverse event can be attributed to the study medication (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this type of medication.
- The event having often been reported in literature for similar types of medication.
- Subject's underlying clinical state or other medical conditions
- Concomitant agents and/or therapies

The causal relationship, if any, to study medication will be defined by one of the following terms:

Assessment	Definition
Definitely	There is suspicion of a relationship between study medication and AE (without determining the extent of probability); there are no other more likely causes and study medication is suspected to have contributed to the AE
Probable	AE cannot be reasonably explained by other factors (i.e. clinical condition, environmental/toxic factors or other treatments)
Possible	AE can be reasonably explained by other factors (as mentioned above)
Unlikely	AE occurs within an unusual time frame of administration of study medication and can also be reasonably explained by other factors (as mentioned above)
Unrelated	There is no suspicion that there is a relationship between study medication and adverse event, there are other more likely causes and study medication is not suspected to have contributed to the AE

9.2.5 Treatment of adverse events:

Treatment of any AE is at the sole discretion of the investigator and according to current available best treatment. The applied measures will be recorded in the patient's chart.

9.3 Criteria for individual subject withdrawal

A subject *must* permanently discontinue study drug treatment for any of the following reasons:

1. The subject becomes pregnant (pregnancy test will be performed for female patients with child bearing potential during each visit). If a patient becomes pregnant, treatment must be *immediately* discontinued. The pregnancy must be reported to the NIB (treating physician/research nurse) and to the IRB immediately. Information about the subject, the subject's pregnancy, the outcome of the pregnancy, and the status of the infant at 8 to 12 weeks of age will also be collected.
2. The subject desires to discontinue study drug treatment under this protocol. Patients have the right to withdraw from the study at any time and for any reason. The investigator also has the right to withdraw patients from the study in the event of an intercurrent illness, adverse events, treatment failure, protocol violations, administrative reasons, or other reasons.
3. 1st MS safety criterion: Worsening of more than two points on the EDSS scale *(Kurtzke 1983)* compared to baseline, confirmed one month later on an extra follow-up visit. The treatment will be discontinued, but the patient will be followed off therapy to collect all predetermined outcome measures as per "intention to treat" analysis.
4. 2nd MS safety criterion: The average number of new CEL (which represents a measure of MS-related brain inflammatory activity) increases after initiation of idebenone therapy 3 standard deviations above the average number of CEL during pre-treatment baseline and IPPoMS trial or for patients with no CEL observed on MRIs collected during baseline period (expected to be the majority of PP-MS patients), the number of CEL recorded on a

single follow-up MRI reaches 10 CEL (total). Treatment will be discontinued, but the patient will be followed off therapy to collect all predetermined outcome measures as per "intention to treat" analysis.

5. Laboratory safety criteria: ALT (SGPT) or AST (SGOT) more than three times the upper limit of normal during regular laboratory monitoring and remains more than three times the upper limit after one week of cessation of idebenone dosing. Any other highly abnormal laboratory finding that is deemed critical by an investigator and that persists for 1 week after cessation of drug dosing.

The reasons for discontinuation of the study drug must be recorded in the subject's Clinical Center patient file. Patients discontinuing dosing will be followed for an additional 2 months. If discontinuation was because of an adverse event, the patient will be followed until the event is resolved or stabilized. If the discontinuation was because of pregnancy, the subject will be followed until after the birth.

10. OUTCOME MEASURES

10.1 Primary outcome measure:

The IPPoMS trial has an adaptive design that will determine the primary outcome measure for the IPPoMS protocol based on pre-determined analysis of the quantitative clinical and neuroimaging secondary outcome measures in the first 30 subjects who finish 1 year of pre-treatment baseline. This analysis is expected to be concluded in the spring/summer of 2013. The primary outcome measure that comes out of the pre-determined analysis in the IPPoMS trial will be adopted as primary outcome measure in the IPPoMS-E trial.

10.2 Secondary outcome measures:

10.2.1 Neuroimaging outcomes:

1. Inhibition of individualized rates of development of brain atrophy: effect of idebenone on individualized rates of development of brain atrophy
2. Inhibition of individualized rates of development of brain gray matter atrophy: effect of idebenone on individualized rates of development of segmented gray matter atrophy
3. Inhibition of individualized rates of enlargement of ventricular volume: effect of idebenone on individualized rates of enlargement of segmented volume of 3rd ventricle
4. Inhibition of individualized rates of development of cervical SC atrophy: effect of idebenone on individualized rates of development of SC atrophy
5. Inhibition of individualized rates of neuroaxonal destruction as assessed by T1 relaxation time in the brain (ROI in normal appearing white matter and in deep gray matter): effect of idebenone on individualized rates of neuroaxonal destruction

6. Inhibition of individualized rates of neuroaxonal destruction as assessed by T1 relaxation time in the cervical spinal cord: effect of idebenone on individualized rates of neuroaxonal destruction
7. Inhibition of individualized changes in axonal integrity as assessed by axial diffusivity and of changes in myelin integrity as assessed by radial diffusivity on brain DTI imaging: effect of idebenone on individualized rates of neuroaxonal destruction

10.2.2 Clinical/functional outcomes:

1. Progression of lower extremity disability as assessed by 25 foot walk component of MSFC (comparing area under curve (AUC) between 1 year of pre-treatment baseline collected during IPPoMS trial and one year of idebenone therapy)
2. Progression of upper extremity/fine motor movements disability as assessed by 9 hole peg test component of MSFC (comparing area under curve (AUC) between 1 year of pre-treatment baseline collected during IPPoMS trial and one year of idebenone therapy)
3. Progression of neurological disability as assessed by MSFC (comparing area under curve (AUC) between 1 year of pre-treatment baseline collected during IPPoMS trial and one year of idebenone therapy)
4. Progression of neurological disability as assessed by Scripps NRS (comparing area under curve (AUC) between 1 year of pre-treatment baseline collected during IPPoMS trial and one year of idebenone therapy)
5. Progression of neurological disability as assessed by EDSS (comparing area under curve (AUC) between 1 year of pre-treatment baseline collected during IPPoMS trial and one year of idebenone therapy)

10.2.3 Biological/immunological outcomes:

1. Analysis of changes in CSF albumin quotient (ROS are known to disrupt endothelial tight junctions; which may be measured as increase in CSF albumin quotient)
2. Analysis of changes in CSF biomarkers of oxidative stress and mitochondrial stress (e.g. 4-HNE, DJ-1)
3. Analysis of changes in CSF lactate, as a biomarker of extra-mitochondrial glucose metabolism
4. Analysis of changes in CSF biomarkers of CNS tissue destruction (e.g. NCAM, OMGP and Contactin-2)
5. Analysis of changes in CSF biomarkers of inflammation (e.g. CXCL13, IL-12p40, sCD27)

10.3. Tertiary/exploratory outcome measures

10.3.1 Neuroimaging:

1. Progression of Fe accumulation in deep gray matter structures of the brain as assessed by quantification of hypointense signal on T2* MRI imaging
2. Progression of retinal nerve fiber thinning as detected by OCT

10.3.2 Clinical:

1. Progression in cognitive dysfunction as assessed by PASAT component of MSFC (comparing area under curve (AUC) between 1 year of pre-treatment baseline collected during IPPoMS trial and one year of idebenone therapy)
2. Progression in cognitive dysfunction as assessed by Symbol Digit Modality Test (comparing area under curve (AUC) between 1 year of pre-treatment baseline collected during IPPoMS trial and one year of idebenone therapy)
3. Progression of neurological dysfunction as assessed by finger and foot tapping (comparing area under curve (AUC) between 1 year of pre-treatment baseline collected during IPPoMS trial and one year of idebenone therapy)

11. STATISTICAL ANALYSIS

11.1 Data acquisition and processing

All clinical, neuroimaging volumetric and biomarker data will be collected sequentially and analyzed in a blinded fashion from coded samples. Data will be acquired prospectively and transcribed to the research database. For the majority of imaging biomarkers the analysis will be performed only after completion of baseline or treatment periods, because the images need to be co-registered to the first acquired image. For biomarker data that can be acquired from cryopreserved biological samples, baseline and treatment data points will be evaluated simultaneously, to limit effect of inter-assay variation. Every effort will be made to have single rater/investigator to acquire one type of quantifiable clinical, neuroimaging and biomarker data for the entire cohort. Statistical analysis will be done by NINDS statistician.

11.2 Statistical analyses of outcome measures

Descriptive methods will be used to analyze the safety data. Generally, for the analysis of efficacy data in IPPoMS-E protocol, we will utilize equivalent outcomes collected during IPPoMS trial.

For primary and secondary outcome measures, we will use identical statistical approach as utilized in IPPoMS trial: i.e. in order to utilize all collected data, we will calculate areas under curve (AUC) values for each outcome, normalized per 1 year of "therapy". Thus, we will calculate AUC for three different "treatments": pre-treatment baseline (B), placebo (Pl) and for idebenone (I) treatment. We will compare intra-individual changes in AUC values by following linear mixed effect model:

$AUC_{outcome}$ = treatment (B, PL, I) + group + interaction between treatment and group + covariates

where "group" refers to original "placebo" versus "idebenone" groups from IPPoMS trial and the random part is patient. While randomization is stratified for age and therefore, we are expecting that the placebo and active treatment groups will be well-matched for age, we will use Age and sex as covariates in the model if we detect any interaction.

In addition to analysis of primary and secondary outcomes, combining data collected during IPPoMS and IPPoMS-E studies will significantly enhance our ability to detect treatment-related changes in CSF biomarkers. Depending on how many subjects choose to participate in IPPoMS-E, the amount of paired (i.e. no treatment versus idebenone) CSF samples may theoretically increase up to 2 fold in comparison to IPPoMS trial. Therefore, the cohort of patients originally assigned to placebo can be utilized as "confirmatory" cohort for biomarker changes identified in the IPPoMS trial. This would effectively increase the power for detecting significant differences, as only those biomarkers found to be significantly changed during the IPPoMS trial would be tested in the IPPoMS-E trial, thus limiting the number of multiple comparisons that would need to be performed (and for which p values need to be properly adjusted). Again, the differences in selected CSF biomarkers between "no-treatment", "placebo" and "idebenone" treatment would be analyzed using the same mixed effect model.

Finally, combining CSF data from IPPoMS with IPPoMS-E will provide two different longitudinal datasets: for patients originally randomized to placebo, we will have three CSF samples off therapy (Mo -1: baseline, Mo 12&24: placebo) and for patients originally randomized to idebenone, we will have three CSF samples (Mo12, 24 and 36). These longitudinal data will allow us to calculate "slope" of progression and compare these slopes between two different treatments using again linear mixed model:

Biomarker = time + treatment + interaction between time & treatment + covariate

where "treatment" is either idebenone or no idebenone (i.e. pre-treatment baseline + placebo). The interaction between treatment and time will assess if the slopes for two treatments are parallel or not. It has been suggested that evaluating changes in the "slope" of progression may distinguish true ongoing neuroprotective effect from static "symptomatic" effect *(Machado, Murray et al. 1999; Ginsberg 2008)*. In other words, under hypothetical scenario that idebenone may prove efficacious in PP-MS, its effect on disability may vary depending on the pathophysiology of the disease. There are two possible scenarios:

1. That idebenone enhances ATP production in neurons, soon after initiation of its dosing, and this enhances electrical conduction in demyelinated axons. The result would be improvement in neurological function. However, if enhancement of ATP production does not also lead to neuroprotection, then the "slope" of progression after initiation of idebenone therapy would be parallel to the "slope" of progression off therapy. In other words, the efficacy on the outcome would be "static" – resetting the baseline, but not changing the "slope" (Figure 3A).
2. That idebenone enhances ATP production in neurons, oligodendrocytes and astrocytes. This may, to some degree, protect all CNS cells from death. As death of neurons and oligodendrocytes continues on a progressive basis, a true neuroprotective drug will inhibit

the slope of the measured outcome (e.g. progression of disability or CNS tissue destruction) in comparison to no treatment. Such dynamic effect would lead to a greater absolute difference in the outcome with greater duration of therapy (Figure 3B). Finally, the drug may have both symptomatic and neuroprotective effects (Figure 3C).

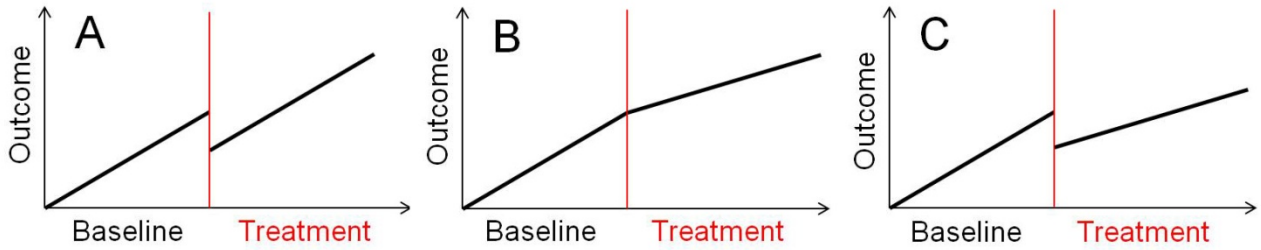

Figure 3:
Possible effects on the outcome (e.g. disability) by static "symptomatic" versus true "neuroprotective" therapeutic

A. Static "symptomatic" effect will "reset the baseline" but will not alter the slope of progression
B. True neuroprotective drug will change the slope of progression, so its efficacy on the outcome (i.e. the absolute difference in comparison to no treatment condition) will increase with the duration of treatment
C. Combination of static and dynamic effect on the outcome by therapeutic that has both symptomatic and neuroprotective effect

Based on this rationale, for CSF biomarkers of CNS tissue destruction (that may be changing in time), we will evaluate the slopes of the change between idebenone and no idebenone treatments.

11.3 Handling of missing/unobtainable data

All efforts will be made to collect a complete set of data by employing 2-4 week flexibility in scheduling and repeating inadequate quality MRI scans.

In the event that particular data points are missing for reasons other than inability to perform the test (i.e. because of disability) we will replace the missing data according to following algorithm:

a. For data obtained every 6 months (i.e. clinical data and brain MRI data), the missing time point will be substituted by the average of 2 adjacent time-points: i.e. 6 months before and 6 months after the missing time-point. If the last time-point is missing (i.e. month 36), we will substitute the data for this time-point by the average of 2 preceding time-points.
b. For data obtained once at treatment phase (i.e. CSF and apheresis data), the missing data cannot be replaced and the patient will be eliminated from analysis.

Handling data missing because the patient was unable to perform the test due to disability: this may happen for clinical tests such as timed 25 foot walk (25FW), 9 hole peg test (9HPT) and PASAT. These data will be calculated using the following recommendations from scoring instructions for the MSFC:

a. 25FW: the inability to perform 25FW will be substituted by the largest Z-score in the MSFC Task force database (i.e. with the slowest time of any patient in the combined dataset used by the Task Force in its published meta-analysis). The largest Z-score in the

Task Force dataset is 13.7, therefore, for a subject who could not complete the 25FW $Z_{leg, average}$ = -13.7 will be used.

b. 9HPT: the inability to perform 9HPT will be coded as 777 and the following Z-score calculation formula will be applied:
$Z_{arm, trial\#}$ = [(1/777 – Baseline mean (1/9HPT)]/Baseline SD (1/9HPT)
c. PASAT: In the event an individual patient cannot complete PASAT-3 due to disability, a score of 0 will be assigned.

11.4 Power analysis and sample size calculation

Sample size and power considerations are not relevant here as this is an open-label extension study design.

11.5 Accrual number request

Because up to 85 patients can be enrolled into IPPoMS study (to yield 66 subjects who complete 2 years of dosing), theoretically up to 85 subjects can be enrolled into IPPoMS-E study.

12. HUMAN SUBJECT PROTECTION

12.1 Subject selection

The investigational nature and objectives of this trial, the procedures and treatments involved, as well as the attendant risks, discomforts, and potential benefits will be carefully explained to the patient. A signed consent form will be obtained by the principal investigator or an associate investigator. It will be carefully explained to patients that they may withdraw from the study at any time, for any reason.

All adult PP-MS patients fulfilling all inclusion criteria and for whom none of the exclusion criteria are applicable, irrespective of gender or race are included in the IPPoMS trial. All patients who conclude IPPoMS trial will be eligible for IPPoMS-E study.

Patients who are unable to give informed consent will be excluded, as these patients were also excluded in the IPPoMS Trial, and therefore will not qualify for this extension trial.

12.2 Justification for exclusion of children

No patients under the age of 18 are included in IPPoMS and therefore this is not relevant to this open-label extension study. Patients under the age of 18 were excluded in the IPPoMS trial since the incidence of MS in this age group is extremely low and PP-MS is virtually non-existent. Consequently, insufficient numbers of patients in that age range would be available to provide reliable data.

12.3 Study safeguards

Because the effects of idebenone therapy on pregnancy and breastfeeding are unknown, patients able to become pregnant or able to father a child will be required to use appropriate methods of contraception for the trial duration and all women able to become pregnant will be evaluated with a pregnancy test every 6 months and before any MRI. Women over age 55 who have not had a period for one year will be considered menopausal and will not need pregnancy testing or contraception. Women under the age of 55 will undergo pregnancy testing and will be required to use appropriate methods of contraception for the trial duration, unless there is a history of surgical menopause.

12.4 Qualifications of investigators

The NIB clinical team has extensive experience with Phase I/II experimental therapeutic trials in MS. This team has performed 7 Phase I/II clinical trials in MS in the past 10 years. The PI, Dr. Bibiana Bielekova is a board-certified neurologist with full clinical privileges. She underwent clinical research training (Core Course in Clinical Research at NIH, October 1997-June 1998, FDA's Clinical Investigator Training Course, November 7-9, 2011) and served as an investigator on 5 Phase I/II clinical trials at NIH and 2 Phase II clinical trials at the University of Cincinnati. She will supervise all aspects of the clinical trial including supervision of all biological and immunological assays. Dr. Bielekova will not obtain informed consent or serve as a treating or evaluating physician due to a conflict of interest.

Lead associate investigator Alison Wichman is a board certified neurologist. She has been credentialed in the NIH Clinical Center continuously since 1982. She has expertise in many aspects of clinical research both as a clinician, and in management roles related to research ethics, regulations, human subject protection, and SOP development. Mary Alice Sandford is a certified nurse practitioner with over 30 years of experience working with patients with neuroimmunological disorders, including Multiple Sclerosis. Dr. Tanya Lehky is a board-certified neurologist with full clinical privileges.

All above-mentioned investigators will have direct clinical contact with patients and all the above associate investigators can obtain informed consent. The Principle Investigator will not obtain informed consent.

Jenifer Dwyer is a registered nurse specialized in MS clinical care. Laura Kannaian is a registered nurse with multiple years of experience including with MS patients. Rosalind Hayden is a registered nurse with experience in research and regulatory support. She will be involved in regulatory submissions, and will also supervise patient scheduling. The above-mentioned investigators will have direct clinical contact with patients and they will not obtain informed consent.

Drs. Wichman, Lehky, and Ms. Sandford will be responsible for patient care and assessment, collection of clinical and functional outcome measures and overseeing clinical safety.

Dr. Bhagavatheeshwaran is a staff scientist with the NIB. Dr. Bhagavatheeshwaran is responsible for MRI acquisition and analysis. Elena Romm is biologist with long-term experience in sample collection and processing. She will supervise collection, processing and storage of all biological

samples: CSF, serum/plasma and apheresis/whole blood samples for PBMC collection. She will serve as the primary laboratory contact and will keep an updated database of biological sample collection and storage. Dr. Bhagavatheeshwaran and Ms. Romm will not obtain informed consent.

13. BENEFITS

13.1 Direct Benefit:

Participants may receive direct therapeutic benefit from participation in this study

13.2 Indirect Benefit:

The study will yield generalizable knowledge about the drug and disease state and will aid in developing future neuroprotective therapeutic trials in MS patients

14. SUMMARY/CLASSIFICATION OF RISK:

Classification of risk for the study as a whole: The risk is classified as more than minimal risk.

This is a reasonable risk in relation to the anticipated potential therapeutic benefit in a patient population for which there are currently no therapeutic agents with proven benefit and for obtaining generalizable knowledge that will facilitate more rapid screening of novel neuroprotective agents in low-inflammatory progressive MS subtypes.

15. CONSENT DOCUMENTS AND PROCESS

Prior to any testing under this protocol, including screening or pre-treatment tests and evaluations, written informed consent will be obtained from the subject in accordance with local practice and regulations. Study investigators (As noted in section 12.4) will obtain informed consent.

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the subject. A copy of the informed consent document signed and dated by the subject will be given to the subject. Confirmation of a subject's informed consent will also be documented in the subject's medical records prior to any testing under this protocol, including screening or pre-treatment tests and evaluations.

Information that is gained through this study will be available to the participating patients.

Consent forms are attached.

16. DATA AND SAFETY MONITORING

16.1 Monitoring plan for the study as a whole

This study will be monitored by a Data and Safety Monitoring Board (DSMB). Dr. Mary Kay Floeter is a board-certified neurologist with full clinical privileges. She will serve as the Independent Medical Monitor. Dr. Floeter is independent of NIB and will be involved in crucial decision making regarding clinical issues that may arise during this trial. We are instituting an NIB independent medical monitor as a way to mitigate Dr. Bielekova's conflict of interest (COI). Dr. Bielekova, the PI on the study, is co-inventor on an NIH patent related to the use of idebenone and as such will receive patent royalty payments.

16.2 DSMB plans

16.2.1. The proposed members of the DSMB are as follows:

We will utilize the same DSMB that is currently monitoring IPPoMS trial: Mitchell T. Wallin, MD (DSMB chair) and Walter Royal, MD from MS Center of excellence, East, VA, Baltimore, MD, Carlos Mora, MD from Georgetown University MS center and Prof. Ludwig Kappos, MD from MS research group, University Hospital Basel, Switzerland

16.2.2. Role of DSMB:

Monitor/review AEs on a yearly basis and SAEs within 7 days of occurrence

16.2.3 Proposed meeting frequency/ schedule:

The DSMB will meet on a yearly basis via teleconference. Yearly AE data and clinical data will be collected and provided to the DSMB for review. Additionally, all SAEs will be communicated to the DSMB within 7 days of occurrence.

16.3 Criteria for stopping the study:

All SAEs will be communicated to the DSMB within 7 days of occurrence. The DSMB will decide on further action.

17. QUALITY ASSURANCE (QA)

17.1 Quality assurance monitor

A Contract Research Organization (CRO) will monitor this protocol.

17.2 Quality assurance plan

On-site monitoring will be carried out by the CRO. An initial visit will be conducted by the CRO, following final approval of the protocol by the IRB and FDA. During the initial visit, the study team and the monitor determined the frequency of monitoring visits. The frequency was set at yearly. The sponsor via the CRO, will be responsible for providing adequate oversight of the investigation

to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data.

18. REPORTING OF UNANTICIPATED PROBLEMS, ADVERSE EVENTS AND PROTOCOL DEVIATIONS

The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with NIH policy, IRB requirements, and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the CD.

Serious unanticipated problems, serious adverse events (including deaths) that are not unanticipated problems, and serious protocol deviations will be reported to the IRB and CD as soon as possible and in writing not more than 7 days after the PI first learns of the event, unless immediate reporting is waived for specific serious adverse events as noted below. Not serious unanticipated problems and not serious deviations will be reported to the IRB and CD as soon as possible and in writing not more than 14 days after the PI first learns of the event. Written reports will be submitted in PTMS.

All adverse events, deviations, and unanticipated problems will be summarized and reported at the time of Continuing Review.

The following expected Serious Adverse Events will not be reported to the IRB immediately and within 7 days unless they occur at a rate or severity greater than expected:
Hospitalization for urinary tract and kidney infections
Hospitalization for falls resulting in injury

These SAE's will be summarized at the time of continuing review. Serious adverse events occurring at a greater severity or frequency than expected will be reported as Unanticipated Problems as delineated above. The expected severity and frequency will be based upon each patient's pre-randomization history (baseline).

The NINDS, holder of the investigator-IND, or her/his representative is responsible for submitting reportable SAEs to the FDA under its private IND application, in accordance with Federal and NIH requirements. When a Serious Adverse Drug Reaction occurs during the clinical trial, the NINDS is also responsible for providing Santhera Pharmaceuticals (Switzerland) Ltd. or designee with a) primary safety information (i.e. short description including at least patient's number, age and gender; reported SAE terms and causality assessment) at the same time the NINDS clinical director and head of IRB are informed and no later than by Day 4 and b) copies of all Serious Adverse Drug Reaction reports concurrently with their submission to the FDA, including copies of any warning letters or other information affecting the safety and/or well-being of human subjects in research conducted under this MCRADA.

Santhera Pharmaceuticals (Switzerland) Ltd. is responsible, in collaboration with UBC Geneva, for the processing of reportable SAEs received from the NINDS or her/his representatives. Santhera is also responsible for the submission of those reportable SAEs to Health Authorities (other than the FDA), Ethics Committees and Investigators taking part in clinical trials with the same investigational

medicinal product, as required by regulations. Moreover, Santhera Pharmaceuticals (Switzerland) Ltd. will transmit to the NINDS all reports of Serious Adverse Drug Reaction occurring in Santhera-sponsored clinical trials and assessed as causally related to the investigational medicinal product, as well as any other information altering the safety profile of the study drug.

19. ALTERNATIVES TO PARTICIPATION OR ALTERNATIVE THERAPIES

There are currently no therapeutic alternatives with proven therapeutic benefit for PP-MS patients.

Idebenone may be able to be obtained on the internet. It is not approved by the FDA for treatment of MS.

20. PRIVACY

All research activities will be conducted in as private a setting as possible.

21. CONFIDENTIALITY

21.1 For medical records:

Medical records will be maintained in the NIH Clinical center and released according to NIH regulations and Health Insurance portability and Accountability Act of 1996 (HIPAA) guidelines.

21.2 For research data:

Research data will be coded and locked in file cabinets if in paper form or in password protected electronic databases maintained on NINDS secure server or on encrypted computers at the NIH. Only study investigators will have access to research data. Coded data and results may be shared with Santhera Pharmaceuticals for research purposes and for drug filing with the FDA.

21.3 For stored samples:

Coded biological samples will be stored in secure freezers and liquid nitrogen tanks at the NIH. Anonymized samples may be made available for future testing in this or other laboratories following the guidelines of the Office of Human Subjects Research.

22. CONFLICT OF INTEREST/TECHNOLOGY TRANSFER

NIH guidelines on conflict of interest have been distributed to all investigators.

Dr. Bielekova has identified a conflict of interest related to this study. She is one of the co-inventors on an NIH patent related to the use of idebenone as therapeutic agents in humans. This conflict of interest is properly disclosed in the protocol and in the consent form.

To resolve this conflict-of-interest, we have instituted following safeguards:

- Dr. Bielekova will not obtain informed consent and will not serve as the treating or evaluating physician on this protocol.
- Mary Kay Floeter, MD, a senior NINDS neurologist who is not part of the NIB, will serve as the Independent Medical Monitor under this protocol.
- The independent DSMB will monitor the study.

No other investigators identified any additional conflicts of interest.

A Cooperative Research and Development Agreement (CRADA) with Santhera Pharmaceuticals has been drafted through the NIH/NINDS office of technology transfer (OTT). This agreement specifies that Santhera will provide idebenone without restriction for the clinical study as outlined and will provide $140,000 supplement for partial coverage (estimated ≥ 50%) of patient travel cost. All collected raw data will be the sole property of NINDS. Summary data will be made available to Santhera Inc. for regulatory purposes and for commercial purposes. Santhera Inc. can use these summary data for other purposes only after consultation with NINDS and only under confidentiality agreement.

23. RESEARCH AND TRAVEL COMPENSATION

Enrolled patients will not be compensated for time and research-related inconveniences.

Enrolled patients will be reimbursed for travel and lodging according to NINDS guidelines (travel form as attachment).

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25. ATTACHMENTS/APPENDICES

APPENDIX A: Flow chart

	Month 24	Month 24 Week 1	Month 25	Month 26	Month 30 (Multiple days)	Month 36 (Multiple days)	Month 37	Final visit
Informed Consent	√							
Inclusion/Exclusion criteria	√							
Clinical evaluation					√	√		√
Urinalysis/pregnancy					√	√		
Safety Lab work			√		√	√		√
Telephone Interview		√	√	√			√	
MRI brain 3T					√	√		√
MRI spine 3T						√		
OCT						√		
Research Blood (≤ 60ml)	√					√		
Apheresis*						√		
Lumbar puncture	√					√		

*120cc of whole blood may be collected if apheresis is unable to be performed, for any reason.

These time points are approximated. To accommodate for patient scheduling needs or clinical necessity, study visits will be accepted within a +/- 4 week window of the time points noted. Biological samples (CSF, whole blood or apheresis sample) should be collected within 4 weeks of the MRI examination as indicated in Figure 2. Blood samples at 24 and 36 months will be collected concomitantly with CSF samples.

APPENDIX B: Eligibility checklist

Inclusion criteria

- ☐ Completion of 3 years in IPPoMS study (protocol 09-N-0197)
- ☐ Able to provide informed consent
- ☐ Willing to participate in all aspects of trial design and follow-up
- ☐ If able to become pregnant or to father a child, agreeing to commit to the use of reliable method of birth control (i.e. hormonal contraception (birth control pills, injected hormones, vaginal ring), intrauterine device, barrier methods with spermicide (diaphragm with spermicide, condom with spermicide) or surgical sterilization (hysterectomy, tubal ligation, or vasectomy) for the duration of treatment arm of the study

Exclusion criteria

- ☐ Clinically significant medical disorders that, in the judgment of the investigators can cause CNS tissue damage or limit its repair, or that would expose the patient to undue risk of harm or prevent the patient from completing the study
- ☐ Pregnant or lactating women. All women of child-bearing potential must have negative pregnancy test prior to the treatment phase of the study.
- ☐ Patients who dropped out of IPPoMS due to AEs considered related to study medication

APPENDIX C: Case Report Forms (CRFs)

In electronic format via CRIS in the structured Neuroimmunology note

APPENDIX D: Rating scales

Expanded Disability Status Scale (EDSS):

0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

Scripps NRS Systems Examined		Maximum points	Normal	Degree of impairment		
				Mild	Mod.	Severe
Mentation and Mood:		10	10	7	4	0
Cranial nerves:	Visual acuity	21	5	3	1	0
	Fields, Discs, Pupils		6	4	2	0
	Eye movements		5	3	1	0
	Nystagmus		5	3	1	0
Lower cranial nerves:		5	5	3	1	0
Motor:	RU	20	5	3	1	0
	LU		5	3	1	0
	RL		5	3	1	0
	LL		5	3	1	0
Deep Tendon Reflexes:	UE	8	4	3	1	0
	LE		4	3	1	0
Babinski: R&L (2 for each)		4	4	-	-	0
Sensory:	RU	12	3	2	1	0
	LU		3	2	1	0
	RL		3	2	1	0
	LL		3	2	1	0
Cerebellar:	UE	10	5	3	1	0
	LE		5	3	1	0
Gait: Trunk and balance:		10	10	7	4	0
Bladder/Bowel/Sexual dysfunction:		0	0	-3	-7	-10
Scripps NRS total score:						

APPENDIX E: Investigator's Brochure

Uploaded in PTMS as pdf file